ANTIBIOTICS MONOGRAPHS | NO 12

Under the Editorial Direction of

Henry Welch Ph D and Felix Martı Ibánez M D

ANTIBIOTICS MONOGRAPHS | NO 12

ANTIBIOTIC THERAPY FOR STAPHYLOCOCCAL DISEASES

Edited by

HENRY WELCH Ph D

Editor in-Chief of Antibiotics & Chemotherapy *and* Antibiotic Medicine & Clinical Therapy *Washington D C*

and

MAXWELL FINLAND M D

Associate Professor of Medicine Harvard Medical School Associate Director Thorndike Memorial Laboratory and Physician in Chief Fourth Medical Service Boston City Hospital Boston Mass

Foreword by Felix Marti Ibáñez M D

A Publication of

MEDICAL ENCYCLOPEDIA INC NEW YORK N Y

Library of Congress Catalog Card Number 59 15374

Printed in the United States of America

Distributors outside U.S.A

Interscience Publishers New York
Interscience Publishers Ltd London

CONTRIBUTORS

Maxwell Finland M D
Associate Professor of Medicine Harvard Medical School, Associate Director Thorndike Memorial Laboratory and Physician in Chief Fourth Medical Service Boston City Hospital Boston Mass

E L Foltz M D
Assistant Professor of Medicine The School of Medicine
University of Pennsylvania Philadelphia Pa

Joseph E Geraci M D
Section of Medicine Mayo Clinic and Mayo Foundation Rochester Minn

William M M Kirby M D
Professor of Medicine University of Washington School of
Medicine Seattle Wash

Felix Marti Ibanez M D
Professor and Director of the Department of the History of Medicine New York Medical College Flower and Fifth Avenue Hospitals New York N Y

Ray A Olsson M D
Senior Resident in Medicine George Washington Medical Division
District of Columbia General Hospital Washington D C

Monroe J Romansky M D
Professor of Medicine George Washington University School of Medicine Chief George Washington University Medical Division District of Columbia General Hospital Washington D C

Henry Welch Ph D
Editor in Chief of *Antibiotics & Chemotherapy* and *Antibiotic Medicine & Clinical Therapy* Washington D C

Ellard M Yow M D
Department of Medicine Baylor University College of Medicine and the Ben Taub Infectious Disease Laboratory Jefferson Davis Hospital Houston Texas

TABLE OF CONTENTS

FOREWORD

It is the fate of each new advance in medical science at once to solve old problems and create new ones which must also be solved before the consolidation and progress of such advance can be finally attained Every time in history the physician makes a great discovery he seems condemned to pay a price for his achievement by having to face new dangers unleashed by such discovery That is what happened to the heroes of ancient mythology each of whose epic achievements brought only a new peril to be faced and a new enemy to be vanquished before the final goal could be victoriously reached

A similar situation happens in therapeutics since every one of its advances is founded on the discovery of new agents to be used on the human being for either or both of two purposes to reinforce the physiological defenses and to destroy the causal agent of the disease In the final analysis the whole complex web of clinical therapy is reduced to these two possibilities In the field of therapeutics the purpose of scientific research and of its practical applications is the physiological restoration of the altered functions of the patient s organism and the elimination of the endogenous or exogenous causal agent of his disease

When a new medication is given to a patient it sets up in his tissues two different series of biochemical reactions those intended to normalize his altered physiology and those aimed at counteracting the etiologic factor When the medication is used against an invading foreign agent as in cases of infection it acts the same as if a monkey wrench had been thrown among the diminutive gears of the delicate metabolic machinery of the germ triggering off a series of reactions Such reactions can lead to a change in the natural history of the disease and of its causal germ and sometimes accomplishes its eventual disappearance At other times a drug provokes defense reactions of such magnitude as to blunt the edge of the medication and stimulate the devel

opment of extremely toxic forms of the infecting germ, which then takes revenge by unleashing huge waves of unusual virulence in the pathogenic ocean of the disease

The problem of the pathogenic reaction to each new therapeutic action has been repeated throughout medical history with the regularity of a pendulum Every fresh advance in the conquest of infection—Pasteur s vaccines Koch s sera Lister s antisepsis and asepsis Ehrlich s magic bullets, Gelmo s sulfonamides Fleming s penicillin—has given rise to a whole host of new problems and perils Like wild mushrooms which lying hidden in the woods seem to spring up suddenly out of nowhere after the stimulating effect of a summer shower these reactions that crop up on the heels of every therapeutic advance are often already latent and waiting only for the stimulus of the new discovery in order to materialize

Antibiotics one of the greatest therapeutic conquests of our time have been continually adding to the sweeping curve of their history making cycle a series of lesser cycles bristling with dangers and difficulties These smaller cycles are related to the potency and the duration of the effect of antibiotic doses and consequently to the reactions of the body and the germs to these drugs

One such reaction to antibiotic therapy has been the emergence of resistant organisms which have survived generations of antibiotic onslaught The problem of antibiotic resistant infections is today the gravest and most imperative of all problems in antibiotic medicine It is all the more serious because it affects not only the individual patient whose life is seriously threatened by such invulnerable germs but also society in general

Dr Henry Welch co author of this book pointed out some years ago in an editorial that was a magnificent piece of scientific detection that infections caused by antibiotic resistant staphylococci were confined almost exclusively to hospitals and therefore were observed only by physicians in charge of hospitalized patients What was at first little more than a scientific curiosity grew in importance and gravity when it spread throughout the nation s hospitals converting many wards almost into gigantic culture broths of such germs whose lair was the throat skin and intestines of hospital personnel hospital equipment and even its walls from which they could fall upon any hospitalized patient exposed to them What at first was a scientific paradox and later a clinical problem thus developed into a public health problem that has been only partially solved

Originally the only way of avoiding such infections was to stay away from the clinical centers where like prowling beasts in a jungle the antibiotic resistant germs permanently lurked But with the increase in the number of hospitals so affected and with ever more individual cases occurring in daily practice the problem overleapt its original limits and has become one of the

most serious to be faced at the present time even by the physician in private practice

Historically this is not a new problem Two centuries ago in a maternity ward in Vienna physicians were faced with the same problem posed by puerperal fever which was taking a mortality toll of 26 per cent Then one day the Hungarian physician Ignaz Philipp Semmelweis deduced its connection with the *Leichengift* or cadaveric poison that clung to the hands of physicians and students when performing autopsies and was then communicated by them to the maternity cases under their care Semmelweis brought mortality down to 1 per cent simply by ordering that all hands be washed in lime water or chloride of lime thus eliminating the source of infection

Of course this situation has nothing in common with the present situation of antibiotic resistant staphylococci except that the puerperal infections also originated inside the hospital and that ironically enough they too were communicated by the very physicians whose duty was to save their patients As things are the germs like birds of prey settling in an impregnable nest have *not only taken up quarters in certain hospitals but have developed complete* protection for themselves against the magic bullets of chemotherapy

Fortunately ceaseless research in antibiotic clinical pharmacology has produced weapons with which to fight these germs until adequate public health measures are adopted to cleanse the infected hospitals

The book we now introduce has been edited by two eminent authorities on antibiotic medicine Dr Henry Welch and Dr Maxwell Finland a happy combination of a famous research scientist and a brilliant clinical investigator each of whose work has brought added luster to the history of antibiotics Five eminent clinicians—Drs Romansky Yow Foltz Kirby and Geraci—have collaborated with them to gather together everything the physician should know about six important antibiotics to be able to use them to the best advantage Some of these products are the outcome of the latest research and show great promise others have a solidly established therapeutic value and all of them—ristocetin kanamycin oleandomycin novobiocin vancomycin and erythromycin—are of great value in combating infections resistant to other antibiotics

In a limpid and terse scientific prose the authors present their points of view and their rich clinical experience with each of the mentioned drugs and recommend how best to use them to overcome the threat to the efficacy of antibiotics This book is invaluable not only because it is the first work to study with full panoramic scope and profound penetration the philosophic and clinical problem of microbial resistance to antibiotics but also because it is a practical guide for the physician in deciding where how when and why to use each one of these drugs successfully in the treatment of the often fatal antibiotic resistant infections

This book therefore crystallizes the physician s answer to one more challenge and the medical action taken against microbial reaction to antibiotics The problem is on the wav to solution Other problems will undoubtedly follow for that is the fate of medical discoveries But the clinical vision thought and experience reflected in this volume and the dynamic and scientific way this tragic episode is being countered give promise that the physician s genius and ingenuity will also vanquish any future threats to his endeavors

FELIX MARTI IBAÑEZ, M D
Professor and Director of the Department of the History of Medicine New York Medical College Flower and Fifth Avenue Hospitals New York N Y

New York N Y
September 1959

Antibiotic Therapy for Staphylococcal Diseases

Chapter I

The Staphylococcal Problem and Effects of Early Antibiotics

Henry Welch
Editor in Chief of *Antibiotics & Chemotherapy* and
Antibiotic Medicine & Clinical Therapy Washington D C

The staphylococcal disease problem now plaguing the entire medical profession both here and abroad is not new It has been with us for ages Recently the Ravenholts[18] discussed this problem in a most comprehensive manner emphasizing that historically staphylococcal infections have occurred endemically and epidemically complicating surgery and childbirth for centuries The authors pointed out that suppuration pyemia and septicemia were the common sequelae of surgery so common was suppuration after surgery in the early days that if delayed in its appearance active measures were employed to hasten the formation of laudable pus That suppuration was neither a necessary nor a desirable product of surgery was demonstrated repeatedly before Pasteur provided the bacteriological key to the puzzle

Early in the eighteenth century a few surgeons of vision recognized the value of isolating such surgical infections in a sanitary environment and many demonstrations were made to show that wounded patients held under crowded conditions inevitably became infected Evidence was presented to show that in large metropolitan hospitals infections were much more common than in small private country hospitals During these early times when the nature of infection was first beginning to be understood the causative organism was no different from what it is at the present time and also then as now hospitals were the dominant source of infections a large proportion of which were probably caused by staphylococci If one reviews the mortality figures from hospital acquired pyemia and septicemia over the years since the middle of the nineteenth century it becomes evident that the mortality rate during that period was not much different from current mortality figures obtained at some

of our large teaching hospitals A review of such data makes one question the proper place of antibiotics in the problem of the resistant staphylococci which were causing their proportion of deaths long before antibiotics became available

The problem of cross infection with staphylococci in a sense is not significantly different from that of the β hemolytic streptococci that caused innumerable deaths from puerperal fever in hospitals before the introduction of the concept of asepsis by Ignaz Semmelweis in Vienna that of antisepsis by Lister in England and the introduction of hygienic measures in hospitals in the United States stimulated by men such as the brilliant Oliver Wendell Holmes Puerperal sepsis was practically eliminated as a cause of death through the efforts of these men and others interested in making hospitalization of expectant mothers safer than childbirth in the home History shows however that death from staphylococcal infections occurred in the days of Semmelweis before his time and is still occurring at present Whereas the β hemolytic *Streptococcus* is a fragile organism quite susceptible to the hazards of its environment succumbing readily to drying heat and light the hemolytic *Staphylococcus* is quite resistant and is not disturbed greatly by such physical forces it survives for long periods of time in dust in the sunlight and on fomites

Through chemotherapy and the process of selection we have further strengthened the resistant staphylococci spawning strains of this organism that not only resist the physical forces that destroy the more fragile streptococci but resist all efforts of many of our miracle drugs the now indispensable antibiotics It must be realized that staphylococci resistant to the antibiotics were in existence both here and abroad long before the discovery of our first useful antibiotic penicillin Many culture collections containing staphylococci isolated prior to 1928 include strains resistant to penicillin these organisms are penicillinase producers A similar situation without doubt exists in so far as other antibiotics are concerned although such resistance is not related to known inactivating enzymes Without doubt the widespread use of antibiotics has pointed up the problem of the resistant staphylococci by eliminating sensitive strains but certainly antibiotics alone cannot be said to be the direct cause of their appearance

Historically in the old days childbirth was probably safer at home than in a hospital—actually it was tantamount to signing the death certificate of a woman in labor to admit her to the crowded ill kept dimly lit dirty dusty hospital improperly operated by a group of frock-coated well meaning physicians What is the situation today in our brilliantly lighted clean tiled wall well-equipped modern edifices heavily staffed with white-coated highly trained physicians? Within the past year certain hospitals in this country have closed their obstetrical services and nurseries because of uncontrollable staphy

lococcal infections other hospitals send mothers and their new babies home as rapidly as possible to avoid such infections

THE ORGANISM

In the hospital environment it can be very important to know the antibiotic resistance pattern and phage patterns of the staphylococci that may have to be coped with in a critical situation

These organisms may be divided broadly into two groups the pigment producing mannitol fermenting coagulase positive *Staphylococcus aureus* (*Micrococcus pyogenes* var *aureus*) and the nonpigmenting *Staphylococcus albus* (*M pyogenes* var *albus*) Although *Staph albus* may cause serious infection under certain circumstances it does so rarely the great majority of staphylococcal infections are caused by *Staph aureus* These organisms are lysed by bacteriophage while the *Staph albus* strains are not this susceptibility to phage lysis makes it possible to identify and classify most of the pathogenic strains

Isolation In the isolation of staphylococci among hospital personnel or from patient carriers it has been found helpful to attempt isolation from the nose Studies have indicated that nose and throat cultures are quite comparable and furthermore in our own studies we have not found that the swabbing of the neck wrists and other surfaces of the body resulted in isolation of more or different strains than could be obtained from the nose Cultures are obtained by inserting into the nose a sterile swab and then streaking onto a Petri plate containing nutrient agar to which has been added 7 5 per cent sodium chloride The excess sodium chloride permits growth of staphylococci and tends to inhibit contaminants Well isolated yellow colonies are picked from the plate and transferred to slant cultures

After isolation the staphylococci are tested for their ability to produce coagulase and thus to coagulate human plasma and biochemically to determine whether they are capable of fermenting mannitol If the cultures are coagulase positive and ferment mannitol they are streaked on blood agar plates to determine the kind and degree of hemolysis The zones of hemolysis are clear showing complete lysis of blood cells surrounding the colonies

Antibiotic Resistance If the cultures of yellow colonies produce coagulase ferment mannitol and cause β hemolysis on blood plates two steps may be taken to classify the organisms further namely determination of sensitivity to the various antibiotics and phage typing The most desirable and accurate sensitivity test is the so-called tube serial dilution technique After incubation overnight those tubes showing no growth indicate complete inhibition of the test organism the last tube showing complete inhibition indicates the minimum inhibitory concentration Through similar tests with each of the anti

GROUP I →	29	52	52A	79	42A	← GROUP IV
GROUP II →	3A	3B	3C	55	44A	
	6	7	42E	47	53	
GROUP III →	54	70	73	75	77	
	80	81	42B			

Fig 1 Arrangement of 23 phage types that is used in the laboratories of the Food and Drug Administration

biotics the resistance pattern of the *Staphylococcus* under test is established The standard disc technique is simpler and if properly carried out with well-standardized discs may be useful but is not so satisfactory since this method is a qualitative rather than a quantitative test In this method a clear zone of growth inhibition is observed around the discs containing antibiotics to which the organism is susceptible when that organism is grown on the surface of an agar plate

Phage Patterns The International Committee on Phage Typing recognizes 23 types of phage for *Staph aureus* The arrangement of these phages in the test is entirely up to the laboratory However the one used in the laboratories of the Food and Drug Administration is that shown in figure 1

After the agar is seeded with the organism under test the 23 phages are spotted using capillary tubes in an arrangement that is the same for each culture The plates are then incubated for from four to five hours at 37 C and left overnight in a refrigerator before reading If the organism is susceptible

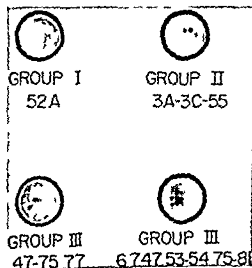


Fig 2 Phage patterns of different types that may be obtained with cultures of *Staph aureus*

to phage all degrees of reactivity from isolated plaques to confluent lysis may be obtained From the pattern established it is possible to separate the phages into three main groups I II and III In figure 2 are shown phage patterns of different types that may be obtained with cultures of *Staph aureus*

Drug resistant staphylococci found in most general hospitals are usually lysed by staphylococcal bacterial phages of group III However in recent years there has been a shift and on occasion we find mixtures of group I and group III phages and the pattern of phage lysis is quite distinct from the usual group III staphylococci Correlation between drug resistance and certain phage patterns is not absolute and exceptions have been reported Knight et al[5] determined phage type of 1543 cultures from 50 physically well patients in a mental hospital in Nashville He found that 55 per cent of these cultures were of the phage type 52/80/81 etc (types 52 and 80 belong to group I and 81 to group III) * Of importance is the fact that 85 per cent of these strains were highly susceptible to penicillin and the tetracyclines Furthermore no serious staphylococcal infections had occurred among these patients in recent years and very little antimicrobial therapy with antibiotics had been used

By comparison the phage groupings obtained by Knight et al in 1953 1954 and 1955 with staphylococci from Bellevue Hospital in New York and the Veterans Administration Hospital in Nashville showed a predominance of group III strains and the great majority of these strains were found resistant to both penicillin and the tetracyclines In both these hospitals antibiotics had been used extensively for treatment

HOSPITAL STAPHYLOCOCCI

Some evidence has been presented that the epidemic type of staphylococcal infection currently encountered in hospitals may be due to drug resistant strains of the 80/81 phage type and the suggestion has also been made that these strains have greater than usual virulence The studies outlined by Knight et al[5] show however that strains of this phage type (80/81) may predominate in a hospital ward in the absence of drug resistance and without the usual staphylococcal infections

The acquisition of drug resistant phage group III staphylococci by implantation while patients are in a hospital apparently occurs readily when such patients are under treatment with antibiotics In a study done at Bellevue Hospital Knight and Holzer[7] treated 25 patients with tetracycline and 30 with penicillin and compared them with 13 patients who were not given antibiotic treatment They showed that the implantation of resistant group III staphylococci occurred quite rapidly in the 25 patients treated with tetra

* Most recent classification

GROUP I	29	52	52A	79	42A	GROUP IV
GROUP II	3A	3B	3C	55	44A	
	6	7	42E	47	53	
GROUP III	54	70	73	75	77	
	80	81	42B			

Fig 1 Arrangement of 23 phage types that is used in the laboratories of the Food and Drug Administration

biotics the resistance pattern of the *Staphylococcus* under test is established The standard disc technique is simpler and if properly carried out with well standardized discs may be useful but is not so satisfactory since this method is a qualitative rather than a quantitative test In this method a clear zone of growth inhibition is observed around the discs containing antibiotics to which the organism is susceptible when that organism is grown on the surface of an agar plate

Phage Patterns The International Committee on Phage Typing recognizes 23 types of phage for *Staph aureus* The arrangement of these phages in the test is entirely up to the laboratory However the one used in the laboratories of the Food and Drug Administration is that shown in figure 1

After the agar is seeded with the organism under test the 23 phages are spotted using capillary tubes in an arrangement that is the same for each culture The plates are then incubated for from four to five hours at 37 C and left overnight in a refrigerator before reading If the organism is susceptible

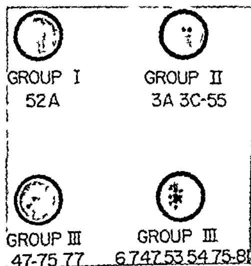


Fig 2 Phage patterns of different types that may be obtained with cultures of *Staph aureus*

are not From the extensive literature now available on staphylococcal disease it is clear that the reservoir of most antibiotic resistant strains is the hospital and that strains from the community at large are predominantly sensitive to the antibiotics Whether this situation can prevail indefinitely is questionable since patients returning from the hospital as carriers to their community will certainly disseminate these strains in their environment

Staph aureus *Versus* Salmonella typhosa At the Sixth Annual Symposium on Antibiotics sponsored by the journals *Antibiotics & Chemotherapy* and *Antibiotic Medicine & Clinical Therapy* a panel discussion was held on staphylococcal disease [31] One of the panel members Phyllis M Rountree of Australia with her colleagues was the first to recognize the staphylococcal disease problem in hospitals Dr Rountree and her colleagues as early as 1948 published studies of hospital outbreaks caused by antibiotic resistant staphylococci and emphasized the epidemic nature of the disease At the symposium Dr Rountree stated that we must remember that staphylococcal disease is an infectious disease No one would dream of leaving *a case of typhoid fever in a medical or surgical ward Until one knows* the actual infection rate in a hospital until one treats this disease as an infectious disease we really will not get very far with its control

It is of some interest to compare the organisms involved The staphylococci may be either parasitic or saprophytic while the typhoid bacillus is always parasitic Staphylococci are resistant to their environment and are not affected materially by light They resist drying for months and are relatively resistant to heat *Sal typhosa* on the other hand is relatively fragile is not resistant to heat and does not survive drying for very long periods of time Both the *Staphylococcus* and *Sal typhosa* are pleoantigenic There are many different antigenic strains of *Sal typhosa* and those who have studied the phage types of the staphylococci recognize the very definite pleoantigenic nature of this organism Both *Sal typhosa* and staphylococci may cause epidemics Epidemics of typhoid fever were controlled mainly by sanitation Certainly drugs were *not involved Strict control of carriers strict isolation of patients with* the disease and strict attention to sanitary precautions were the key to the control of this disease

The strict isolation of patients with staphylococcal infections would be difficult in many of our hospitals Certainly the small suburban hospital would be hard put to find space to isolate all persons with staphylococcal infections in as strict a manner as one would unhesitatingly isolate a patient with typhoid fever Yet certainly this must be the ultimate goal if adequate control of staphylococcal disease is to be obtained Fortunately typhoid carriers are few and far between whereas staphylococcal carriers are abundant both in the hospital environment and in the community at large There seems to be no doubt however that the focus of staphylococci is in the hospital

cycline within four to five days 85 per cent of the patients had acquired the resistant hospital strain The acquisition of resistant strains in the penicillin treated group of 30 patients was somewhat slower They pointed out that this may have been due to the fact that in this group 50 per cent of the strains isolated at the time of admission to the hospital were penicillin resistant Thus treatment with penicillin suppressed a smaller percentage of the admission (resistant) strains than did tetracycline consequently providing less opportunity for replacement with hospital staphylococci However over a period of about eight to nine days the flora of the 13 patients who were not treated with antibiotics changed little and few resistant staphylococci were isolated

Further evidence of implantation of drug resistant staphylococci in hospital patients has been reported by Knight et al[8] from the Veterans Administration Hospital in Nashville Before administration of tetracycline the patients under study carried very few strains of staphylococci resistant to this drug and few also of the multiple drug-resistant group III staphylococci After the patients received tetracycline however strains susceptible to tetracycline disappeared and these were replaced by the drug resistant hospital staphylococci Within seven to nine days nearly complete replacement occurred This change resulted from suppression of a high percentage of tetracycline susceptible strains by treatment with the drug leaving the nose throat and other carrier sites free for implantation of the hospital staphylococci Among the patients receiving no treatment replacement was much more gradual requiring some 30 days and resulting in an increase of only about 10 to 30 per cent of implanted strains during this period of time Hospital personnel reacted like untreated patients in that they acquired drug resistant strains at a slow rate

There seems to be no doubt that disease producing staphylococci frequently implant in the nasal pharynx without producing overt disease Thus we have in the population at large a high percentage of carriers of potentially dangerous staphylococci The probability is that the carrier rate of such staphylococci is a good index of the level of contamination that one finds in the environment From studies made in the laboratories of the Food and Drug Administration it would appear that the coagulase positive *Staph aureus* carrier rate is on the order of 60 per cent Many hospitals in the past year or two have had serious problems with *Staphylococcus* infections and throughout the country all hospitals have a potential problem It would seem an advisable procedure since time may be of the essence in certain of these outbreaks of staphylococcal disease that sensitivity tests and phage typing be done on all the prevailing organisms in a given hospital community such information could be of considerable value in a critical situation Although there are a large number of staphylococci that are capable of producing infection many are susceptible to the presently available antibiotics although obviously some

therefore transient hand carriers could be a problem where organisms travel from nose to hand to infant It seems likely that contamination by droplets expelled into the air is also a source of transmission of staphylococcal disease Contamination of skin by infected clothing bedding and other fomites likewise perpetuates spread of the organism

Looking at the staphylococcal disease problem objectively one cannot escape the fact that although it has many facets in common with contagious diseases such as typhoid fever it is immeasurably more complicated and will be infinitely more difficult to bring under control The greater resistance of the staphylococci the large number of carriers of this organism the manner *in which it is acquired and the difference in susceptibility of the host to* infection (controllable in the case of *Sal typhosa*) all militate against easy solution Furthermore the increase in number of geriatric patients now in hospitals along with the greater life span of the debilitated and the diabetic patient and the high susceptibility of infants to staphylococcal infection further magnify the problem

In spite of the fact that the indiscriminate use of antibiotics has been said by many to be responsible for our staphylococcal disease problem there is no scientific evidence that this is the case At best the antibiotics may have pointed up a situation already in existence for centuries by eliminating the sensitive staphylococci Certainly in so far as the epidemic disease is concerned history indicates that it has been cyclic in character without regard to chemotherapy Furthermore it is difficult to explain why an epidemic occurs in a single hospital in a city and not in the others when the policy of antibiotic usage is not markedly different in any of them unless one comes to the obvious conclusion that there has been a breakdown in technique allowing dissemination of a hot strain

In such a situation failure to withhold one or more of the antistaphylococcal antibiotics such as has been done in some areas could not have been held responsible for the initiation of the epidemic or for its perpetuation The withholding of these antibiotics for treatment when a critical situation arises (an epidemic) does not seem very realistic when there are at least nine possible antibiotics available for staphylococcal infections and individual cases of these infections far outnumber the epidemics If a hospital chooses to restrict the use of certain antibiotics because of toxicity or because of the possibility of increasing the incidence of strains resistant to them the use of these antibiotics should be permitted in individual patients when they are the agents of choice for the particular infections involved

ANTIBIOTICS AVAILABLE FOR STAPHYLOCOCCAL INFECTIONS

In addition to the six antibiotics that are discussed in detail in separate

and that if dissemination is to occur it will occur from this focus Carriers of hospital staphylococci are presently leaving the hospital and carrying the organisms into their home environments In some instances the carriers will lose the organisms after they have been in their home environments for vary ing periods of time their flora will then be replaced with the so-called normal environmental flora On the other hand a number of these persons will continue to carry the hospital strains of staphylococci for many months It is likely that mothers implanted with hospital staphylococci may return in a year or more for another delivery still carrying the strain they originally acquired in the hospital This situation according to Dr Rountree has already occurred in Australia

Sources of Infection The cause or source of continuing hospital infections is frequently difficult to trace Although it can be assumed that infections definitely pass from infant to mother to environment to infant and so on it is not easy to find and break the chain In an epidemic reported[3] from a small town in New Jersey where a number of infants became infected and passed the infection to a large percentage of the mothers many changes in the handling of the infants in the nursery were instituted infected cases were isolated wet mopping of the nursery was instituted and filtration and treatment of air with ultraviolet light was initiated Since infection in the newborn infant occurs usually after the third day infants were checked and sent home on the third day In addition all personnel known to be carriers were taken off duty in the nursery and all linens clothing and other fomites were sterilized before washing Through such procedures the epidemic was slowed down but not stopped It was later found that a part time worker in the nursery was a permanent carrier of the 52/42B/80/81 strain as soon as she was relieved from duty the epidemic ended This situation is certainly reminiscent of the pattern of an epidemic of typhoid fever

The many ways that an epidemic of staphylococcal disease can be per petuated is uncertain but the same is true of epidemics of typhoid fever The epidemiologist usually must study epidemics of typhoid fever intensively to find the carrier or the source of contamination and then prevent perpetuation of the epidemic by eliminating the source or carrier In the case of staphylococcal disease personnel carriers in hospitals have definitely been implicated in some outbreaks Furthermore several epidemics have been controlled by finding and eliminating such carriers In some epidemics reported in the literature control by use of antibiotics has been accomplished while on the contrary it has failed in others probablv because of the emergence of new resistant strains of staphylococci In some outbreaks transfer of the infection from infant to infant has appeared to be important and certainly the infected infant transmits the organism to and without a doubt infects the nursing mother A staphylococcal organism is definitely resistant to its environment and

localize and then exude spontaneously Such cases today are seen mainly in private practice and not in the hospital environment

Penicillin should probably not be used topically for minor skin infections This is not because of lack of efficacy of this drug but rather because of its high sensitizing potential In addition there are available several antibiotics of the polypeptide type of low sensitizing potential that are quite as effective as penicillin for this purpose Penicillin can be used orally where desirable in such infections as an adjunct to other topical therapy

BACTEREMIA The prognosis in staphylococcal bacteremia was uniformly poor in the presulfonamide era The incidence of recoveries increased with sulfonamide therapy and the situation improved considerably after the use of penicillin the fatality rate dropping approximately 15 to 25 per cent under proper use of this agent Most strains of staphylococci encountered in private practice are still sensitive to low or moderately high concentrations of penicillin and the best results in cases of bacteremia are obtained when treatment is started early It is important to use large and adequate dosages because staphylococci have a pronounced tendency to become resistant and this may be accentuated when inadequate dosages are used Patients with *Staph aureus* bacteremia sometimes show little or no objective improvement for as long as a week after treatment has been started In some instances signs of improvement may be evident several days before the temperature finally falls to normal and before blood cultures become negative It is important therefore that treatment be continued until all signs and symptoms of infection have subsided

Intensive therapy must be used to obtain satisfactory results If treatment is started early the dosage should be 500 000 to 1 000 000 units of crystalline penicillin in solution daily given intramuscularly in divided amounts at 2 to 3 hour intervals If a repository form of penicillin is used 600 000 units every 8 to 12 hours is advisable If larger dosages are necessary crystalline penicillin solutions may be given by continuous intravenous infusion and several million units a day may be administered by this method

In all cases of staphylococcal bacteremia the possibility of a metastatic spread must constantly be kept in mind The urine should be examined regularly and signs and symptoms referable to the lungs brain endocardium and other organs should be carefully evaluated If response to intensive penicillin therapy is not satisfactory sensitivity studies should be repeated not only to that drug but to the other antibiotics as well and the plan of therapy adjusted accordingly

OSTEOMYELITIS It is now well established that penicillin if started early in the course of acute osteomyelitis caused by sensitive staphylococci often results in complete recovery in most cases without the need for surgical drainage As soon as the diagnosis is reasonably certain 200 000 units of

chapters in this book penicillin chloramphenicol the tetracyclines and bacitracin all have been and still are useful for some of the staphylococcal infections Leucomycin now in use in Japan also appears to have merit in this field This antibiotic is now under clinical study in this country and preliminary in vitro work indicates it to be quite active against *Staph aureus* but it will not be considered in detail in this volume

Penicillin Penicillin of course has been used in staphylococcal infections and it still is according to data presented at the Sixth Annual Symposium on Antibiotics In a panel discussion on antistaphylococcal antibiotics moderated by Maxwell Finland there was general agreement that penicillin would be the drug of choice in infections caused by susceptible strains (strains susceptible to 2 0 units or less per ml) There was general agreement also that if the infecting strain is a penicillinase producer (and thus resistant) high dosages are usually of little avail and the panel recommended against its use in such cases However some experts not represented on that panel expressed themselves in favor of the use of massive dosages in severe infections with resistant strains and have observed good effects from such usage in their experience

In considering the use of penicillin for infections caused by staphylococci sensitive to this drug a distinction should be made between hospital acquired disease and that acquired in the community or home environment The infections acquired in the hospital are nearly always caused by penicillin resistant organisms and thus this drug alone or in combination with other antibiotics is generally of little avail Those infections acquired outside a closed environment are frequently sensitive to penicillin and it is the drug of choice in such infections Sensitivity studies of the infecting organism are of course essential for proper handling of these cases

TOXICITY Penicillin probably still is the least toxic (inherently) of the antibiotics available This should be kept in mind with those patients who are susceptible to treatment with it particularly when other antibiotics perhaps equally effective but more toxic could also be used The toxicity of penicillin is related to its antigenicity and proclivity for sensitization in certain persons Where the possibility of sensitivity or sensitization can be obviated penicillin is one of the most useful drugs in staphylococcal infections due to penicillin susceptible organisms and this is most often the case in infections acquired outside the hospital environment

PENICILLIN IN STAPHYLOCOCCAL INFECTIONS STAPHYLOCOCCAL INFECTIONS OF THE SKIN AND SOFT TISSUES Penicillin has been used successfully in a great number of cases of furunculosis and other forms of pyoderma including carbuncles and abscesses where sensitive organisms are involved With systemic treatment healing of the lesions without incision or drainage often results within a day or two The purulent material may undergo resolution or

therapy in daily amounts of from 1 000 000 to 2 000 000 units or more by intermittent intramuscular injections at two hour intervals or the drug may be given by continuous intravenous infusion In infants or children 10 000 units of crystalline penicillin are given intrathecally once or twice daily combined with 50 000 to 200 000 units or more every two hours parenterally Simultaneous administration of sulfonamides with penicillin according to some workers gives better results than penicillin alone and they recommend regimens employing both drugs The dosage of sulfonamide should be ample to maintain a blood concentration of approximately 10 mg /100 ml Treatment should continue for a minimum of three weeks

STAPHYLOCOCCAL ENDOCARDITIS Staphylococcal endocarditis is the most serious complication of generalized staphylococcal sepsis and carries the poorest prognosis However Wilhelm et al[30] observed recoveries in 6 of 11 patients treated with penicillin Staphylococci usually cause an acute malignant form of endocarditis Occasionally however where a strain of low virulence is involved the disease follows a subacute course In the usual acute form multiple septic foci are often present Infarcts in the spleen lungs and brain are common and the valvular lesions are only one feature of the generalized sepsis When the disease follows a subacute course the infection localizes at endocardial sites for several weeks after which meningitis and other septic complications may occur Large dosages of penicillin are usually needed in treatment 500 000 units or more of soluble penicillin every six hours or 600 000 units of procaine penicillin every 12 hours should be used and this regimen should be continued for from four to eight weeks Because of the relatively low recovery rate sensitivity determinations to the other antibiotics and sulfonamide drugs are advisable and should be used as a guide to therapy in all cases Multiple antibiotic therapy may be quite successful when response is unsatisfactory or when a relapse occurs Penicillin and streptomycin are reported to have been used successfully in this infection as well as penicillin and bacitracin when the infecting organism is sensitive to these antibiotics At the present time penicillin is still clearly the drug of choice for the treatment of staphylococcal endocarditis when the infecting organism is sensitive to this drug

STAPHYLOCOCCAL OTITIS MEDIA AND MASTOIDITIS The value of penicillin in the treatment of these infections is well established when susceptible organisms are involved Penicillin should be started in the early acute phases when it often obviates the need for surgical intervention The usual dosage is 200 000 units of soluble penicillin every six hours or 600 000 units of procaine penicillin twice daily If surgical drainage becomes necessary it should be done without delay The results obtained in chronic infections are in general less satisfactory than those observed in the more acute cases

Chloramphenicol The first report on the drug chloramphenicol (Chloro

penicillin every four hours should be injected intramuscularly or if a repository form of penicillin is used 300 000 to 600 000 units every 12 to 24 hours should be given If treatment is delayed beyond a few days considerable bone destruction occurs with necrosis of the cortex and cavity formation This requires surgical drainage Surgery is necessary also if there is abscess formation either subperiosteal or in the soft tissues or where the joint space is invaded In these cases parenteral therapy may be supplemented with local instillations of a soluble salt of the drug in a concentration of 5000 units or more per ml This is usually repeated once or twice daily

In chronic osteomyelitis penicillin gives highly satisfactory results but only when combined with adequate surgical intervention Sequestra must be removed early and sinus tracts excised before healing can occur Treatment with penicillin for three to six weeks or longer is usually required If the response is not satisfactory or if a relapse occurs repeat bacteriological studies should be done to determine the sensitivity of the organism involved to the available antibiotics and the plan of treatment should be revised in accordance with the findings Treatment failures may occur if one antibiotic is used when another is actually indicated

STAPHYLOCOCCAL PNEUMONIA Primary as well as secondary cases of staphylococcal pneumonia have responded favorably to penicillin when the organism was sensitive If there are no foci elsewhere recovery may be complete within a week or two with intensive penicillin therapy The drug must be administered in large amounts (250 000 to 500 000 units) every two to three hours intramuscularly or by continuous intravenous infusion The patient should receive the same general symptomatic care as in other types of pneumonia The more common complications include staphylococcal empyema pericarditis and lung abscess Many cases of staphylococcal pneumonia occur in hospitalized patients who may be infected with resistant strains of this organism in such cases penicillin is not the proper antibiotic to use and sensitivity tests must be performed to determine the best antibiotic treatment

STAPHYLOCOCCAL MENINGITIS If staphylococcal meningitis caused by a sensitive strain is treated early and intensively the recovery rate is approximately 40 per cent Surgical measures to permit free drainage of the primary focus or foci of infection are essential Treatment should be continued for at least 10 days after the signs and symptoms of meningitis have subsided and repeated cultures of the cerebrospinal fluid are negative Recurrences have been reported as late as four to six weeks after therapy was discontinued Penicillin is given intrathecally as well as systemically The dosage of crystalline penicillin G intrathecally is 20 000 units given in a volume of 5 ml once or twice daily The repository types of penicillin are not recommended in this infection The intrathecal administration is combined with systemic

In spite of this however in some subjects chloramphenicol can be demonstrated in low concentrations at the twenty fourth hour

Chloramphenicol diffuses readily into the cerebrospinal fluid and other body fluids and indirect evidence suggests that it also penetrates cells of the body in the form that has antibacterial activity The antibiotic is metabolized presumably in the liver and appears in both the bile and saliva after administration

TOXICITY Chloramphenicol is a drug of remarkably low toxicity The literature indicates that the great majority of investigators who have studied this drug clinically reported no untoward reactions Smadel [1] pointed out that in spite of the nitrobenzene nucleus in the formula of chloramphenicol which might suggest toxicity for the erythropoietic system in man he had not observed any evidence of intolerance or toxicity in a relatively large number of patients with high dosages In addition to this Woodward and his colleagues[3] have treated 200 typhoid patients and approximately 1500 additional patients with varied infectious disorders and in no instance did they encounter evidence of the serious blood dyscrasias reported by other investigators

Early in 1950 a few reports appeared implicating chloramphenicol as the cause of certain blood dyscrasias These and subsequent publications have made it evident beyond reasonable doubt that in certain susceptible persons chloramphenicol causes blood dyscrasias including aplastic anemia leukopenia thrombocytopenic purpura and granulocytopenia Of these female children under 12 years of age with a history of chronic illness asthma or allergy are most frequently affected

Occasionally other untoward reactions minor in character have been recorded Hirsch [5] in reporting the effect of chloramphenicol in a case of infectious mononucleosis stated that his patient complained of an altered sense of taste food lost its flavor and smoking was not pleasant The second side effect was the dramatic appearance of a sensitivity response which occurred on the sixth day of treatment At this time the patient felt somewhat dizzy his face became flushed and red macular lesions appeared over his face The pulse and respiratory rates were accelerated There was no associated pruritus These symptoms persisted for about 30 minutes and subsided spontaneously The same syndrome occurred after the last dose of the drug was given Stomatitis has been reported as a possible side reaction to chloramphenicol by Robinson et al [19]

These authors in their studies of the effect of chloramphenicol in early syphilis observed stomatitis in 4 of 17 patients In addition they reported some looseness of stools or diarrhea in 1 patient Two patients in their series showed unexplained miliary papular eruptions on the forehead Romansky et al [20] in a study of the antitreponemal effect of oral chloramphenicol ob

mycetin*) by Ehrlich et al was a cautious review of the antibacterial spectrum and apparent low toxicity of this drug Evidence was presented to show that this antibiotic was effective against certain gram negative bacteria such as *Brucella abortus Escherichia coli Klebsiella pneumoniae Proteus* species *Salmonella schottmulleri Shigella paradysenteriae sonnei* and the gram positive organism *Staph aureus* In addition marked chemotherapeutic activity was shown in chick embryos against certain rickettsiae and in embryonated eggs and mice against a virus infection At the same time Smadel and Jackson reported a rather remarkable chemotherapeutic effect of this drug on a number of rickettsiae and on the psittacosis virus Smadel et al [3] later made a careful comparison of the effect of synthetic chloramphenicol and that produced by fermentation and found that chemotherapeutic activity was identical against both rickettsial and virus infections in man and animals At the present time all chloramphenicol is produced synthetically

Clinical indications for chloramphenicol based on laboratory *in vitro studies* have been *in* a large part borne out by actual clinical trial A voluminous literature has accumulated emphasizing the wide antimicrobial spectrum of this drug In a general way it can be said that chloramphenicol really a wide spectrum antibiotic is active against both gram positive and gram negative bacteria certain rickettsiae spirochetes and viruses Fungi and protozoa are not sensitive to chloramphenicol Particular attention is called to its activity against *Sal typhosa* since chloramphenicol unquestionably is the drug of choice in the treatment of typhoid fever Of particular interest is the fact that the very great majority of the so-called resistant staphylococci are susceptible to its action

ABSORPTION AND EXCRETION Chloramphenicol is rapidly absorbed from the intestinal tract of man It is metabolized readily and excreted by way of the kidneys Present evidence indicates that approximately 90 per cent of the administered dose may be accounted for in the urine at the end of 24 hours However less than 10 per cent of the administered dose is excreted unchanged i e in the antimicrobially active form whereas the great bulk of the drug is excreted as an inactive nitro compound

Although lower concentrations of active chloramphenicol are demonstrated in the urine during the oral use of this drug blood concentrations are somewhat higher than those obtained after comparable oral doses of the tetracyclines The concentration of active chloramphenicol in the blood drops off rapidly so that by the sixth hour its concentration is somewhat lower than that obtained at this time with similar doses of the tetracyclines The more rapid disappearance of chloramphenicol from the blood may be explained by the fact that it is rapidly metabolized into the inactive nitro compound

* The trade name of Parke Davis & Co Inc for chloramphenicol is Chloromycetin

these strains have been implicated in epidemics of impetigo and other skin infections Chloramphenicol has been used with success in the management of this type of infection Although furuncles when small and sparse and un complicated do not usually require antibiotic therapy large lesions surrounded by more extensive areas of cellulitis benefit from systemic administration of appropriate antibiotics Response to antibiotics alone may often be disappoint ing in the presence of abscess formation Frequently organisms isolated from these avascular lesions are found quite sensitive to the antibiotic administered even though poor results are obtained Obviously an important part of the management of large furuncles and abscesses is surgical treatment of the con dition by drainage of pus removal of necrotic tissue and possibly enzymatic debridement Chloramphenicol has been employed successfully in the manage ment of localized staphylococcal infections when surgical drainage has been a part of the treatment

STAPHYLOCOCCAL PNEUMONIA AND EMPYEMA Nearly all cases of staphy lococcal pneumonia are caused by hemolytic strains of coagulase positive *Staph aureus* This disease may occur as a primary infection and is seen frequently in infants or as a terminal event in diabetic debilitated or aged persons It occurs as a secondary infection due to chronic pre-existing disease such as chronic pulmonary disease blood dyscrasias or fibrocystic disease and may follow influenza It occurs as a complication or as a superinfection in patients who are being treated orally with the tetracyclines The mortality rate in staphylococcal pneumonia is very high even though chemotherapy is instituted without delay and in adequate dosage In any case to be effective chemotherapy must be instituted promptly if a desirable result is to be obtained There is some evidence that staphylococcal toxins may play a role in the pathogenesis of this disease Toxins already formed would continue to act unabated even though the antibiotic were effective in eliminating the etiological agent The formation of abscesses introduces difficulties in man agement and prolonged administration of the proper antibiotic is necessary to eliminate staphylococci from such lesions and to prevent relapse

The organism involved in the infection frequently exhibits a broad range of antibiotic resistance However most strains causing pneumonia are still found to be sensitive to chloramphenicol when tested in vitro In spite of these favorable in vitro results and the fact that chloramphenicol has been found by some to exert a favorable action in this disease others have reported that their results have not been striking As a matter of fact a number of authors have commented on the apparent ineffectiveness of all the broad spectrum antibiotics in staphylococcal pneumonia this is especially true if abscess for mation is advanced Because of this chloramphenicol alone is not usually indicated in the treatment of this rapidly progressing frequently fatal infection The drug should probably be used in combination with a bactericidal anti

served a mild Jarisch Herxheimer reaction They felt that this reaction was less frequent in patients treated with chloramphenicol than in those treated with penicillin Stephens [4] reported a shock type reaction characterized by circulatory collapse in typhoid patients treated with chloramphenicol Unlike the Herxheimer reaction the temperature was usually depressed

In general fewer cases of loose stools and diarrhea are reported with chloramphenicol than with the tetracyclines An explanation of this in part at least may be the rapid absorption of chloramphenicol from the gut and the rapid inactivation of that remaining in the intestine

In summary the majority of side reactions that occur in man after the administration of chloramphenicol are mild in degree and regress after cessation of the drug Toxic manifestation may be grouped into three cat gories gastrointestinal allergic and blood dyscrasias Fortunately all three complications are rare and are not restricted to this drug alone As has been pointed out by Woodward and Wisseman [33] In our experience chloramphen icol has been well tolerated and there has been no need to discontinue it because of alterations in the hematological picture or other side reactions indicative of renal or hepatic damage Nevertheless the drug should not be used when there is evidence of development of significant anemia, throm bocytopenia or marked granulocytopenia

CHLORAMPHENICOL IN STAPHYLOCOCCAL INFECTIONS Emergence of staphylococci resistant to chloramphenicol has rarely occurred since the de velopment of this drug except in an occasional clinic where it has had wide use in a closed population However the incidence of resistant strains still remains relatively low In most hospitals at the present time some 60 to 80 per cent and even more of the staphylococci isolated are still sensitive to chloramphenicol This continued ensitivity of the staphylococci to chlor amphenicol may be related to the comparatively restricted and more careful use this drug has enjoyed since it was demonstrated that in certain rare in stances it caused various types of blood dyscrasias Regardless of the causes that have been responsible for the low proportion of strains resistant to chloramphenicol the fact is that this drug still remains high on the list of antibiotics that are currently useful in the treatment of staphylococcal infec tions particularly when used together with other more active antistaphylo coccal antibiotics to which the organisms may develop resistance rapidly such as streptomycin erythromycin and novobiocin It should be borne in mind that chloramphenicol is a bacteriostatic drug for most strains of staphy lococci although there have been reports of bactericidal action with certain strains

STAPHYLOCOCCAL INFECTIONS OF THE SKIN AND SOFT TISSUES The *Staphylococcus* is known to be an important cause of impetigo contagiosa Fre quently infections are caused by organisms classified in phage group III and

these strains have been implicated in epidemics of impetigo and other skin infections Chloramphenicol has been used with success in the management of this type of infection Although furuncles when small and sparse and uncomplicated do not usually require antibiotic therapy large lesions surrounded by more extensive areas of cellulitis benefit from systemic administration of appropriate antibiotics Response to antibiotics alone may often be disappointing in the presence of abscess formation Frequently organisms isolated from these avascular lesions are found quite sensitive to the antibiotic administered even though poor results are obtained Obviously an important part of the management of large furuncles and abscesses is surgical treatment of the condition by drainage of pus removal of necrotic tissue and possibly enzymatic debridement Chloramphenicol has been employed successfully in the management of localized staphylococcal infections when surgical drainage has been a part of the treatment

STAPHYLOCOCCAL PNEUMONIA AND EMPYEMA Nearly all cases of staphylococcal pneumonia are caused by hemolytic strains of coagulase positive *Staph aureus* This disease may occur as a primary infection and is seen frequently in infants or as a terminal event in diabetic debilitated or aged persons It occurs as a secondary infection due to chronic pre-existing disease such as chronic pulmonary disease blood dyscrasias or fibrocystic disease and may follow influenza It occurs as a complication or as a superinfection in patients who are being treated orally with the tetracyclines The mortality rate in staphylococcal pneumonia is very high even though chemotherapy is instituted without delay and in adequate dosage In any case to be effective chemotherapy must be instituted promptly if a desirable result is to be obtained There is some evidence that staphylococcal toxins may play a role in the pathogenesis of this disease Toxins already formed would continue to act unabated even though the antibiotic were effective in eliminating the etiological agent The formation of abscesses introduces difficulties in management and prolonged administration of the proper antibiotic is necessary to eliminate staphylococci from such lesions and to prevent relapse

The organism involved in the infection frequently exhibits a broad range of antibiotic resistance However most strains causing pneumonia are still found to be sensitive to chloramphenicol when tested in vitro In spite of these favorable in vitro results and the fact that chloramphenicol has been found by some to exert a favorable action in this disease others have reported that their results have not been striking As a matter of fact a number of authors have commented on the apparent ineffectiveness of all the broad-spectrum antibiotics in staphylococcal pneumonia this is especially true if abscess formation is advanced Because of this chloramphenicol alone is not usually indicated in the treatment of this rapidly progressing frequently fatal infection. The drug should probably be used in combination with a bactericidal anti

biotic to obtain the most satisfactory results In addition when large abscesses are present surgical drainage may be a necessary adjunct to any chemotherapy when the abscess does not communicate with the trachea Removal of exudate from the pleural cavity by thoracentesis is an important part of the therapy of staphylococcal empyema and is invariably used in conjunction with appropriate antibiotic therapy Occasionally closed or even open thoractomy is required to establish proper drainage

STAPHYLOCOCCAL SEPTICEMIA AND ENDOCARDITIS Staphylococcal septicemia with or without associated endocarditis is a disease with an extremely high mortality rate Next to the nonhemolytic streptococci the staphylococci probably cause endocarditis more often than any other organism Endocarditis is probably the most serious complication of generalized staphylococcal sepsis and invariably carries a poor prognosis the course is usually acute but a subacute course is sometimes observed In the usual acute form multiple septic foci are often present The institution of antibiotic therapy does not cause a dramatic reduction in mortality rate from staphylococcal sepsis The increase in number of antibiotic resistant staphylococci has probably been partly responsible for the failure to reduce the fatality rate materially However even though in some cases the organisms causing this serious disease are susceptible to the antibiotics patients still die in spite of antibiotic treatment

There are a large number of penicillin resistant staphylococci causing this disease that are sensitive to chloramphenicol when tested by the usual in vitro test In general however although chloramphenicol occasionally brings about cures it frequently fails to control the infection Evidence seems to show that the best results are obtained when chloramphenicol is employed in combination with another antibiotic such as bacitracin or erythromycin In any case when another antibiotic is used with chloramphenicol such a drug should be bactericidal rather than bacteriostatic Response to therapy seems to be best when it is initiated early in the disease From experience it is apparent that intensive and prolonged therapy is required to obtain complete recovery and recovery is facilitated if the accessible suppurative necrotic foci are drained

OSTEOMYELITIS A large majority of cases of osteomyelitis are caused by staphylococci and a common form is the acute hematogenous variety occurring almost exclusively in children The disease may follow injury to the bone from a fall or bump or may occur as an aftermath of trauma such as a compound fracture Antibiotics have revolutionized the management of acute hematogenous osteomyelitis for in them we have specific means for treatment of both the generalized infection as well as the localized infected process of the bone Local and supportive measures are important in the treatment of this disease and should be started as early as possible The bone should be

immobilized as long as signs of infection persist Prolonged therapy is required to eradicate the infectious process and to prevent relapse and chemotherapy should be integrated with surgical procedures as they may be essential for cure The general objective of surgical intervention includes the eradication of walled off persistent foci increased contact of the therapeutic agent with the affected area and prevention of damage to important structures

Although penicillin has been the drug of choice for the treatment of osteomyelitis caused by staphylococci infection with penicillin resistant strains of the organism has necessitated the use of other antimicrobial agents Chloramphenicol has yielded good therapeutic results in a number of cases despite the fact that it is largely bacteriostatic in action In a general way the treatment of osteomyelitis with chloramphenicol should be considered in (1) the presence of penicillin resistant strains and (2) combined therapy—chloramphenicol with one of the bactericidal drugs such as bacitracin erythromycin or kanamycin

In summary the incidence of chloramphenicol resistant strains at the present time is low and indications for this drug are more frequent than previously It is quite evident that superficial and localized infections caused by organisms sensitive to chloramphenicol tend to respond well to its use When the drug is employed in the treatment of staphylococcal septicemia however its effect is often irregular and disappointing In such serious infections chloramphenicol when combined with other carefully selected drugs chosen on the basis of sensitivity tests particularly if these drugs are bactericidal compares favorably with other antibiotics When there are large accessible foci of suppuration therapy is more successful when proper surgical drainage procedures are used along with chemotherapy In most of the staphylococcal infections prolonged antibiotic administration is essential if relapse is to be prevented

Tetracyclines The tetracyclines are primarily bacteriostatic agents they are bactericidal in relatively high concentrations only All three have been shown in vitro and in vivo to be active against both gram positive and gram negative organisms as well as certain of the large viruses and *Rickettsia* Certain differences in activity may be demonstrated among them e g the apparent greater in vitro activity of chlortetracycline over its analogues against certain of the staphylococci and the demonstrated activity of oxytetracycline in human tuberculosis when both chlortetracycline and tetracycline are apparently ineffective However in a general way the three tetracyclines are equally effective in the great majority of susceptible diseases

ABSORPTION AND EXCRETION The tetracyclines are readily absorbed from the intestinal tract when administered orally in capsule form After absorption they diffuse into all body fluids and tissues In single doses of from 0 75 to 1 0 Gm demonstrable serum concentrations are obtained quite rapidly and

these are maintained for relatively long periods of time Therapeutic levels (for susceptible infections) are maintained rather constantly for from six to eight hours and complete disappearance from the circulation is not observed for from 24 to 30 hours When doses of 0 5 to 1 0 Gm are administered to patients every six to eight hours the serum concentrations of these drugs vary from 2 to 4 μg /ml although concentrations in some patients may exceed 6 or even 8 μg /ml From the blood stream the tetracyclines readily pass into the peritoneal fluid bile urine and milk These drugs have been found in the liver kidney lung and spleen and also pass into the fetal circulation through the placenta Both chlortetracycline and tetracycline pass the blood brain barrier probably in therapeutic amounts The presence or absence of *inflammation is probably not a factor controlling this diffusion as apparently* is the case with oxytetracycline which does not readily traverse the barrier

After oral administration all three tetracyclines appear in the urine in fairly high concentration during the first two hours and stay at maximum concentration for from 6 to 12 hours About 10 to 20 per cent of these drugs is recovered in the urine in the first 12 hours while the amount excreted during the second 12 hours varies considerably

TOXICITY The tetracyclines are chemotherapeutic agents that may be used without fear of serious toxic effects Untoward side effects consist of nausea vomiting epigastric distress heartburn and diarrhea which occur more often in women than in men Nausea and vomiting are controlled in some patients by giving the capsules with milk The diarrhea often persists for several weeks but may be helped by the administration of kaolin pectin or bismuth The diarrhea observed in patients treated with the tetracyclines is probably not a toxic manifestation of these drugs but rather an expression of the profound effect they have on the intestinal flora Several clinical studies have indicated that at the same dosages tetracycline is less likely to cause untoward side effects than its analogues

Other side effects that have been reported after the use of the tetracyclines are stomatitis cheilosis skin and mucous membrane eruptions and vaginitis In addition a Herxheimer type of reaction has been observed Often patients treated with the tetracyclines over a period of time may show nothing but pure cultures of yeast in the stools Frequently the stools become loose and lose their normal odor and the patient complains of pruritus ani The latter is probably due to the abnormal shift of the bacterial flora to the acid producing yeasts

Although the tetracyclines are for the most part used orally some intramuscular and intravenous dosage forms are available Intramuscularly they cause considerable irritation and the site may become extremely painful The intravenous forms *even with the special diluents* may cause phlebitis *in* approximately 10 per cent of patients treated This reaction subsides promptly

without serious residual effect as soon as this method of administration is stopped In those patients treated intravenously the oral dosage form should be substituted as soon as feasible Both nausea and vomiting have been reported after the intravenous use of the tetracyclines and excessive intra venous dosage of chlortetracycline and oxytetracycline and to a lesser degree tetracycline sometimes cause liver damage This is evidenced by jaundice enlargement of the liver and necrotic changes in the cells The liver damage appears to be reversible if administration of the drug is stopped soon enough

The tetracyclines like most drugs will sensitize some persons Extensive clinical use indicates however that the incidence of patients who become sensitive to these drugs is extremely low

TETRACYCLINES IN STAPHYLOCOCCAL INFECTIONS The tetracyclines have been used successfully in a wide variety of staphylococcal infections and it would appear that when the infecting organisms are sensitive these drugs may still be used with success However the distinct tendency for staphylococci to become resistant to these antibiotics makes it essential particularly in the more serious infections to have sensitivity tests performed on the infecting strain This would be particularly true in the hospital community where tetracycline resistant staphylococci are frequently encountered There is almost complete cross resistance among the three tetracyclines and nearly all hospital staphylococci resistant to them are also resistant to penicillin

The tetracyclines have been used with favorable results in local abscesses cellulitis pyoderma acne impetigo otitis media urinary tract infections osteomyelitis staphylococcal pneumonia and bacteremia However in the serious infections it seems apparent that the tetracyclines are best reserved to be used in combination with other agents when the organism is sensitive to them rather than to use them alone since development of resistance is a serious problem in their use Such combinations would be of one of the tetracyclines and penicillin when the organism involved is susceptible to mod erate amounts of penicillin and small or moderate amounts of the tetracycline Similarly erythromycin in combination with one of the tetracyclines would appear logical when the *Staphylococcus* involved is moderately sensitive or sensitive to both drugs

Bacitracin The first report on bacitracin by Johnson et al[6] noted marked antibacterial action particularly against gram positive bacteria *Staph aureus* pneumococcus types I II and III β hemolytic streptococci and certain strains of clostridia were all inhibited in their growth by the action of this drug Bacitracin has little or no activity against the gram negative types except for *Hemophilus influenzae* type B meningococci and gonococci Certain of the actinomycetes and *Treponema pallidum* are sensitive to bacitracin while fungi such as *Candida albicans* *Cryptococcus hominis* and *Nocardia asteroides* are resistant In general organisms sensitive to bacitracin do not readily develop

these are maintained for relatively long periods of time Therapeutic levels (for susceptible infections) are maintained rather constantly for from six to eight hours and complete disappearance from the circulation is not observed for from 24 to 30 hours When doses of 0 5 to 1 0 Gm are administered to patients every six to eight hours the serum concentrations of these drugs vary from 2 to 4 μg /ml although concentrations in some patients may exceed 6 or even 8 μg /ml From the blood stream the tetracyclines readily pass into the peritoneal fluid bile urine and milk These drugs have been found in the liver kidney lung and spleen and also pass into the fetal circulation through the placenta Both chlortetracycline and tetracycline pass the blood brain barrier probably in therapeutic amounts The presence or absence of inflammation is probably not a factor controlling this diffusion as apparently is the case with oxytetracycline which does not readily traverse the barrier

After oral administration all three tetracyclines appear in the urine in fairly high concentration during the first two hours and stay at maximum concentration for from 6 to 12 hours About 10 to 20 per cent of these drugs is recovered in the urine in the first 12 hours while the amount excreted during the second 12 hours varies considerably

TOXICITY The tetracyclines are chemotherapeutic agents that may be used without fear of serious toxic effects Untoward side effects consist of nausea vomiting epigastric distress heartburn and diarrhea which occur more often in women than in men Nausea and vomiting are controlled in some patients by giving the capsules with milk The diarrhea often persists for several weeks but may be helped by the administration of kaolin pectin or bismuth The diarrhea observed in patients treated with the tetracyclines is probably not a toxic manifestation of these drugs but rather an expression of the profound effect they have on the intestinal flora Several clinical studies have indicated that at the same dosages tetracycline is less likely to cause untoward side effects than its analogues

Other side effects that have been reported after the use of the tetracyclines are stomatitis cheilosis skin and mucous membrane eruptions and vaginitis In addition a Herxheimer type of reaction has been observed Often patients treated with the tetracyclines over a period of time may show nothing but pure cultures of yeast in the stools Frequently the stools become loose and lose their normal odor and the patient complains of pruritus ani The latter is probably due to the abnormal shift of the bacterial flora to the acid producing yeasts

Although the tetracyclines are for the most part used orally some intramuscular and intravenous dosage forms are available Intramuscularly they cause considerable irritation and the site may become extremely painful The intravenous forms even with the special diluents may cause phlebitis in approximately 10 per cent of patients treated This reaction subsides promptly

recovered in the cerebrospinal fluid after large intramuscular injections in the absence of inflamed meninges

BACITRACIN IN STAPHYLOCOCCAL INFECTIONS INFECTIONS OF THE SKIN Bacitracin has been used in treating a number of pyodermas including carbuncles and furuncles Meleney and Johnson[10] reported on the treatment of several kinds of pyogenic infections of varied etiology with bacitracin The drug was administered in 100 cases either in aqueous solution (57 cases) in a water soluble ointment base (32 cases) or in a combination of both (11 cases) Furuncles and carbuncles as well as deep or superficial abscesses in the series were treated by injection of the aqueous material into the center of the lesion The quantity used depended on the size of the lesion and varied from 0 1 to 5 0 ml The first injection often caused a burning sensation which tended to become less noticeable with subsequent injections Open ulcers usually were treated with the ointment preparation The drug was considered of value if it obviated or permitted less extensive surgery than would be expected shortened healing time or permitted earlier primary or secondary closure The most important criterion was prompt elimination of the causative organism It was found that bacitracin met one or more of these criteria in 88 per cent of the cases and the authors were impressed by the action of bacitracin against many penicillin resistant strains of staphylococci and nonhemolytic streptococci No evidences of toxicity were observed

Derzavis et al[1] treated 138 patients afflicted with a variety of deep and superficial pyodermas with bacitracin ointment (1000 units/Gm of petrolatum) The response was prompt and effective in all instances when direct contact with the ointment was obtained An extremely low incidence of drug sensitivity was observed

Bacitracin for topical application or for local infiltration is generally used in a concentration of 500 units/ml For open lesions infiltration therapy may be supplemented with moist dressings of the drug or the ointment (500 to 1000 units/Gm) may be used Bacitracin must be put in contact with the invading organisms for optimal results When the drug is used repeatedly for local infiltration or used on extensive denuded areas the possibility of systemic absorption and renal injury should be kept in mind

STAPHYLOCOCCAL PNEUMONIA AND EMPYEMA Bacitracin has been used successfully in a few cases of staphylococcal pneumonia when the organism involved was found resistant to other therapy Although insufficient work has been done to evaluate the role of bacitracin in this disease it may be life saving in some cases but it is most useful when given together with other active antibiotics to which the organism is also sensitive It may be used systemically to supplement large dosages of penicillin if the organism is only slightly sensitive to the latter and it may be used for intrapleural instillations in empyemas due to penicillin resistant strains

resistance to it in vivo, although it is possible to demonstrate this phenomenon in vitro

Bacitracin is a stable drug and at temperatures less than 56 C its stability parallels that of penicillin At temperatures of 80 C it loses potency rapidly As the purity of bacitracin is increased toward its theoretical potency of approximately 70 units/mg, its stability tends to decrease Two relatively insoluble salts of bacitracin zinc bacitracin and bacitracin methylene di salicylate have been made available Both of these salts are more stable in the dry state than is bacitracin and produce far more palatable preparations when used in troches and tablets

TOXICITY There is little doubt concerning the toxicity of bacitracin This toxicity has been demonstrated in animals and in man However, although animal tests invariably show the drug to be nephrotoxic when given in sufficient dosage and for proper lengths of time the drug can be given to man in effective dosage without demonstrable nephrotoxicity Meleney a co discoverer of this drug has made a number of reports[9 11 15] on several hundred cases in which no signs of serious nephrotoxicity were evident He pointed out that the most important safeguard in the intramuscular use of bacitracin is adequate intake of fluids In adults a daily intake of 2500 ml of fluids and an equivalent amount in children is essential All intake and output of fluids should be measured and if urinary output exceeds 1000 ml there need be no fear of nephrotoxicity

The dosage of bacitracin according to Meleney, should be started at 15 000 to 20 000 units and continued every six to eight hours This dosage can be increased to 25 000 units but should not exceed this amount nor should it be used more frequently than four times daily (total 100 000 units) Bacitracin should be used promptly when the infecting organism is found to be resistant to penicillin and sensitive to bacitracin It should probably be used in penicillin resistant staphylococcal infections in preference to the broad spectrum antibiotics because of its bactericidal action and is most useful in combination with other antibiotics to which the *Staphylococcus* is also sensitive

ABSORPTION AND EXCRETION Bacitracin is absorbed quite readily after intramuscular injection but it disappears from the blood less rapidly than penicillin it is not absorbed from the gastrointestinal tract Higher and more prolonged blood concentrations are obtained after intramuscular bacitracin than with comparable doses of penicillin This difference in blood concentration is related to the difference in rates of urinary excretion of these antibiotics Bacitracin is cleared by the kidney at a rate approximating that of glomerular filtration After intramuscular injection in man bacitracin is readily distributed into pleural and ascitic fluids whereas only traces are found in the peritoneal and cerebrospinal fluids In general the drug is not

frequent estimations of renal function and nitrogen retention are necessary When these precautions are observed bacitracin can be both valuable and lifesaving A good therapeutic result can be anticipated if the organisms isolated are sensitive in vitro to less than 1 unit/ml

A number of cases of staphylococcal endocarditis have been treated successfully by Volini and Kadison [8] and Friedberg and Bader [4] These authors usually used the drug in combination with other antibiotics and reported cures in some patients The best chance for cure was related to early treatment and the administration of multiple antibiotics in maximum dosage

OSTEOMYELITIS Meleney et al [15] in a coordinated study reported successful results in a few patients with both acute and chronic osteomyelitis treated with bacitracin While some of these patients received bacitracin only others had failed to respond to other antibacterial agents In general the results in early osteomyelitis were better than those obtained in the more chronic cases In chronic osteomyelitis the best results were obtained when the drug was administered both intramuscularly and by instillation into the wound

Chemotherapy in osteomyelitis should be integrated with surgical procedures and since the incidence of bacitracin resistant staphylococci is currently low indications for the use of this drug may be more frequent Bacitracin therapy may prove to be extremely valuable in chronic osteomyelitis caused by penicillin resistant strains particularly as a second drug along with other active ones

MENINGITIS AND INTRACRANIAL INFECTIONS Five of 6 patients with staphylococcal meningitis who had failed to respond to other antibiotic therapy were reported [6] to be cured with bacitracin These patients were treated by both the intramuscular and the intrathecal routes Treatment consisted of the intrathecal injection of 5000 to 20 000 units and the intramuscular injection of 40 000 to 80 000 units of bacitracin daily The drug was reported to be well tolerated

SURGICAL INFECTIONS Meleney et al [15] in a review of 270 cases largely surgical infections for which bacitracin was administered intramuscularly enumerated 62 pure or mixed staphylococcal infections Of these 62 bacitracin therapy had no effect in 11 In the great majority of all infections bacitracin gave good to excellent therapeutic results These authors also used bacitracin topically in the form of an ointment or solution in 100 cases of superficial surgical infections and obtained excellent to good results in 85

Pulaski and Connell[17] reported treatment of 26 patients with a variety of pyogenic infections with bacitracin The drug was used in dosages of 40 000 to 100 000 units daily intramuscularly Staphylococci streptococci and some gram negative rods were isolated from these cases of cellulitis abscesses and infected wounds The clinical response was good in 16 cases while in 7 there was no effect

STAPHYLOCOCCAL BACTEREMIA Meleney et al[15] reported treatment of 3 cases of staphylococcal bacteremia with bacitracin The first 2 patients were children and both had bacteremia with acute osteomyelitis of the femur The first of these received large dosages of penicillin later combined with sulfa diazine without improvement On the fourth day when the causative organ ism was identified sulfadiazine was discontinued and bacitracin started at a dosage of 20 units/Kg (5250 units) every six hours The next day this dosage was doubled and the signs and symptoms rapidly subsided A slight rise in nonprotein nitrogen was observed which fell to normal during the *treatment period There was evidence that penicillin and bacitracin acted* synergistically in this case

The second patient 10 years of age first received penicillin (100 000 units every three hours) and sulfadiazine (0 5 Gm every four hours) for four days without benefit During this time there had been a slow but progressive development of a mass in the popliteal space and the blood culture revealed a hemolytic *Staph aureus* which was resistant to penicillin but susceptible to bacitracin Treatment was then changed to bacitracin and there was a rapid symptomatic improvement The popliteal mass decreased in size without sur gical drainage and roentgenographic studies showed evidence of gradual heal ing

The third patient was an infant 6 weeks of age with staphylococcal bac teremia and meningitis with metastases in the lungs and subcutaneous tissues Both penicillin and streptomycin had been given without any appreciable effect These drugs were given intrathecally also and later chlortetracycline was used but failed to control the infection Bacitracin was then administered The dosage used was 400 units/Kg of body weight every six hours intra muscularly The drug was given intrathecally also (500 units twice daily) and was instilled by means of a catheter into an abscess of the face The response was dramatic and the patient recovered completely The duration of bacitracin therapy was 15 days and during the first eight days the drug also was given intraspinally Penicillin was used as well during the entire treatment period Since the advent of erythromycin and the more recent antistaphylo coccal antibiotics bacitracin has been used in *Staphylococcus* bacteremias primarily as a second drug to increase the bactericidal action or to prevent the rapid development of resistance It is rarely used as the sole antibiotic in these or other serious infections It is however used for local instillation into focal suppurative lesions

STAPHYLOCOCCAL ENDOCARDITIS Since bacitracin is predominantly bacteri cidal it would appear to be well suited for therapy in bacterial endocarditis In the presence of renal damage such as focal embolic glomerular nephritis which usually accompanies this disease its nephrotoxicity would be more pronounced Thus when bacitracin is used in the treatment of endocarditis

3 FEKETY F R BUCHBINDER L SHAFFER E L GOLDBERG S PRICE H P AND PYLE L A Control of an outbreak of staphylococcal infections among mothers and infants in a suburban hospital Am J Pub Health *48* 3 298–309 1958
4 FRIEDBERG C K AND BADER M E Acute staphylococcic endocarditis cured with the aid of bacitracin J A M A *147* 46–49 1951
5 HIRSCH F G Infectious mononucleosis Report of a case treated with chloromycetin U S Nav M Bull *49* 1081 1949
6 JOHNSON B A ANKER H AND MELENEY F L Bacitracin a new antibiotic produced by a member of the B subtilis group Science *102* 376 1945
7 KNIGHT V AND HOLZER A R Studies on staphylococci from hospital patients I Predominance of strains of Group III phage patterns which are resistant to multiple antibiotics J Clin Investigation *33* 1190–1198 1954
8 KNIGHT V WHITE A AND HEMMERLY T The effect of antibiotics on staphylococci of hospital patients Proceedings of the National Conference on Hospital Acquired Staphylococcal Disease Atlanta Ga Sept 15–17 1958 Atlanta Ga U S Department of Health Education and Welfare Public Health Service Bureau of State Services Communicable Disease Center 1958 pp 39–54
9 MELENEY F L Bacitracin Practitioner *176* 56–61 1956
10 MELENEY F L AND JOHNSON B Bacitracin therapy first 100 cases of surgical infections treated locally with antibiotic J A M A *133* 675–680 1947
11 MELENEY F L AND JOHNSON B A Bacitracin Am J Med *7* 794–806 1949
12 MELENEY F L AND JOHNSON B A Present status of bacitracin available for systemic (intramuscular) administration *In* Antibiotics Annual 1953–1954 New York Medical Encyclopedia Inc 1954 pp 251–260
13 MELENEY F L AND JOHNSON B A A review of systemic bacitracin therapy U S Armed Forces M J *6* 834–842 1956
14 MELENEY F L JOHNSON B A AND TENG P Further experiences with local and systemic bacitracin in treatment of various surgical and neurosurgical infections and certain related medical infections Surg Gynec & Obst *94* 401–425 1952
15 MELENEY F L LONGACRE A B ALTEMEIER W A REISNER E H JR PULASKI E J AND ZINTEL H A Efficacy and safety of intramuscular administration of bacitracin in various types of surgical and certain medical infections with analysis of 270 cases Surg Gynec & Obst *89* 657–683 1949
16 MUNTHE FOG C V Further studies on reduction of the intestinal flora prior to surgery of the colon or rectum Acta chir Scandinav *106* 325–338 1953
17 PULASKI E J AND CONNELL J F JR Bacitracin in surgical wound infections Bull U S Army M Dept *9* 141–147 1949
18 RAVENHOLT R T AND RAVENHOLT O H Staphylococcal infections in the hospital and community Hospital environment and staphylococcal disease Am J Pub Health *48* 3 277–278 1958
19 ROBINSON R C V FOX L M AND DUVALL, R B Effect of chloramphenicol in early syphilis Am J Syph Gonor & Ven Dis *33* 509 1949
20 ROMANSKY M J OLANSKY S TAGGART S R AND ROBIN E D The antitreponemal effect of oral chloromycetin in 32 cases of early syphilis in man a preliminary report Science *110* 639 1949
21 SMADEL, J E Clinical use of the antibiotic chloramphenicol (Chloromycetin) J A M A *142* 315 1950
22 SMADEL, J E AND JACKSON E B Chloromycetin an antibiotic with chemotherapeutic activity in experimental rickettsial and viral infections Science *106* 418 1947
23 SMADEL J E JACKSON E B LEY H L JR AND LEWTHWAITE R Comparison of synthetic and fermentation chloramphenicol (chloromycetin) in rickettsial and viral infections Proc Soc Exper Biol & Med *70* 191 1949
24 STEPHENS P R Unsuccessful treatment of typhoid fever with *chloramphenicol* Lancet *1* 731 1950
25 TENG P Further experiences in treatment of septic meningitis with bacitracin Arch Neurol & Psychiat *64* 861 1950
26 TENG P AND MELENEY F L The treatment of staphylococcic meningitis Surgery *28* 516–533 1950
27 TURNER S J WACKER, M H GOLDIN M AND AUERBACH H Effect of bacitracin suppositories on the vaginal flora and on morbidity in vaginal hysterectomies Am J Surg *82* 498–503 1951

Bacitracin was employed preoperatively by Turner et al [7] in 70 patients who underwent vaginal hysterectomy There was a striking reduction in the number of gram positive cocci diphtheroids and lactobacilli in the vaginal flora after the use of vaginal suppositories containing 10 000 units of bacitracin Postoperative morbidity was markedly reduced in the bacitracin treated group as compared with controls No untoward effects were encountered

PREOPERATIVE PREPARATION OF THE BOWEL Since bacitracin has a narrow antibacterial spectrum and suppresses only the gram positive organisms of the intestinal flora after oral administration it should not be used alone for preoperative preparation of the large bowel Welch et al [9] found that a combination of 5000 units of bacitracin 200 000 units of polymyxin B and 250 mg of streptomycin taken orally four times daily resulted in virtual elimination of coliform bacteria and fecal streptococci A combination of 3 Gm of neomycin and 3 Gm of bacitracin daily was administered by Munthe Fog[16] for three or four days to 32 patients In more than 80 per cent of these cases the intestinal flora was entirely suppressed except for yeast and *Bacteroides* Lower dosages of these combined drugs were not so effective Poorly absorbed drugs such as bacitracin streptomycin polymyxin and neomycin should be ideally suited for preoperative preparation of the bowel particularly since they can be administered in highly bactericidal combinations

Bacitracin may also be useful in staphylococcal enterocolitis which may develop during treatment with broad spectrum antibiotics It is helpful in preventing symptoms of this disease if given when an overgrowth of staphylococci is noted in the feces

In summary bacitracin is a bactericidal antibiotic frequently found to be effective in the treatment of penicillin resistant and tetracycline resistant staphylococci Nephrotoxicity can be kept to a minimum if the intramuscular dosage does not exceed 80 000 to 100 000 units daily given in doses of 20 000 to 25 000 units every six hours Hypersensitivity to bacitracin is extremely rare either as a primary form or as a result of treatment This drug acts in the presence of blood pus and necrotic tissue and has proved effective when injected locally into staphylococcal lesions or joints Bacitracin has been demonstrated to have significant synergistic action against certain organisms when used together with penicillin or erythromycin and should therefore be combined with these drugs in the treatment of mixed infections when sensitivity tests so indicate

BIBLIOGRAPHY

1 DERZAVIS J L RICE J S AND LELAND L S Topical bacitracin therapy of pyogenic dermatoses *J A M A* *141* 191–192 1949
2 EHRLICH J BARTZ, Q R SMITH R M JOSLYN D A., AND BURKHOLDER P R Chloromycetin a new antibiotic from a soil actinomycete Science *106* 417 1947

Chapter II

Current Status of Erythromycin and Monopropionyl Erythromycin

Joseph E Geraci
Section of Medicine Mayo Clinic and Mayo Foundation Rochester Minn

Erythromycin was introduced in 1952 [7] Since then it has had extensive laboratory and clinical investigation Subsequently two detailed reviews of information about it have appeared [5, 17] The present discussion summarizes current knowledge of erythromycin and presents some data on a new mono propionyl ester of erythromycin (Ilosone*)

CHARACTERISTICS AND ACTION

Erythromycin derived from *Streptomyces erythreus* [7] is effective against certain microorganisms [13, 16] It is a basic substance poorly soluble in water but very stable The chemical structure apparently is that of a polyhydroxy ketolactone having the molecular formula of $C_{37}H_{67}NO_{13}$ [38] Erythromycin is more active in an alkaline medium some tenfold increase in activity occur ring per unit increase of *p*H [13] Its activity is apparently not affected by a wide variety of agents including serum that interfere with the action of penicillin and streptomycin [13, 16]

The antibacterial spectrum of erythromycin which resembles that of peni cillin covers many gram positive organisms particularly staphylococci How ever although erythromycin is effective against some gram negative organisms such as *Neisseria* and *Hemophilus* it is of little value against other gram negative bacteria Its chief value has been against infections caused by staphylococci that are resistant to other more commonly used antibiotics such

* The trade name of Eli Lilly & Co for erythromycin propionate is Ilo one It was placed on the market in October 1958

28 VOLINI I T AND KADISON E R Simultaneous bacitracin and penicillin therapy in subacute bacterial endocarditis Report of three cases Am Pract & Digest Treat *2* 13–17 1951
29 WELCH H RANDALL W A AND PRICE C W The effect of streptomycin bacitracin polymyxin combination polymyxin B and streptomycin with glucuronolactone on the intestinal flora of man J Am Pharm A *34* 486–489 1950
30 WILHELM F HIRSH H L HUSSEY H H AND DOWLING H F The treatment of acute bacterial endocarditis with penicillin Ann Int Med 26 221–230 1947
31 WISE R I MODERATOR Causation prevention and control of staphylococcal disease in hospitals (panel discussion) *In* Antibiotics Annual 1958–1959 New York Medical Encyclopedia Inc 1959 pp 1073–1091
32 WOODWARD T F SMADEL J E AND PARKER R T The therapy of typhoid fever M Clin North America *38* 577 1954
33 WOODWARD T E AND WISSEMAN C L JR Chloromycetin (chloramphenicol) Antibiotics Monographs no 8 New York Medical Encyclopedia Inc 1958 p 32

COMBINED USE OF ERYTHROMYCIN AND OTHER ANTIBIOTICS

The in vitro data on combined antibiotic action involving erythromycin may be summarized as follows Only rarely does erythromycin enter into synergistic combination with penicillin tetracycline or chloramphenicol However it does combine with streptomycin and bacitracin to give bactericidal effects on a number of strains of staphylococci [33] Organisms extremely resistant to streptomycin were not killed by the erythromycin streptomycin mixture However the combination of erythromycin and bacitracin was not so limited in effect and was often bactericidal for staphylococci intensely resistant to penicillin and streptomycin [33] The behavior of erythromycin in combination with the bactericidal agents is unpredictable [8] and seems to depend to some extent on the sensitivity of the test organism to the bactericidal agent However the only way to find out whether erythromycin will enter into synergistic combination with another antibiotic agent is to determine the bactericidal activity of the combination in vitro[5] or to make the bactericidal test with serum obtained from a patient being actively treated with the combined agents [7]

The last mentioned test gave the following results in 16 patients treated with erythromycin in combination with another antibiotic for moderately severe staphylococcal infections caused by penicillin resistant organisms [8] With four strains penicillin and erythromycin produced no greater bactericidal effect than did penicillin alone indeed in one test the combination gave no total bactericidal effect whereas penicillin alone gave a total bactericidal effect in a serum dilution of 1 2 Erythromycin and bacitracin gave a synergistic bactericidal effect in three of six strains of staphylococci Erythromycin or bacitracin alone gave no total bactericidal effect but the combination gave such an effect in a serum dilution of 1 4 or greater With three strains neither erythromycin nor bacitracin alone nor the combination gave any total bactericidal effect and apparently bacitracin did not enhance the effect of erythromycin The combination of erythromycin and streptomycin gave enhanced bactericidal effect with one strain but not with two others With two strains erythromycin and chloramphenicol had no total bactericidal effect alone or in combination In one instance the combination of erythromycin and novobiocin gave synergistic bactericidal effects In all instances the serum of these 16 patients gave no total bactericidal effect when tested with erythromycin alone [8]

DOSAGE

Erythromycin is usually administered orally in a dosage of 400 to 500 mg every six hours It can also be given intravenously intramuscularly by aerosol [24, 25] or by instillation into the pleural cavity [6] A dosage as high as

as penicillin tetracycline and streptomycin Clinically erythromycin is predominantly bacteriostatic but at times it may be bactericidal With the usual oral dosage of 400 or 500 mg every six hours the patient s serum achieves only a bacteriostatic effect in tests against most strains of staphylococci [34] Whether erythromycin is bactericidal or bacteriostatic in vitro apparently depends on the sensitivity of the organism the concentration of the antibiotic and the maturity of the culture [14] The antibiotic is active against rapidly multiplying organisms but has little effect on mature cultures [34] For some organisms such as *Corynebacterium diphtheriae Hemophilus pertussis* and a few strains of staphylococci it may be bactericidal but with most strains of staphylococci and nonhemolytic streptococci it is merely bacteriostatic [9] In general its killing effect is not rapid and is quite variable [16]

Petersdorf and colleagues[3] found that the bactericidal end point (minimal bactericidal concentration) for staphylococci that were sensitive to erythromycin was uniformly high For only a few of the many strains of staphylococci that they tested was the bactericidal end point the same as or close to the bacteriostatic end point (about 1 in 10)

DEVELOPMENT OF RESISTANT STRAINS OF BACTERIA

Erythromycin shows no cross resistance with the other more commonly used antibiotics [18] However with erythromycin like antibiotics there is a variable cross resistance [6, 1, 31] For organisms isolated from clinical material there is almost complete cross resistance with carbomycin Partial and variable cross resistance occurs with oleandomycin and spiramycin For organisms rendered resistant in the laboratory there is almost complete cross resistance among all of these agents [6, 21, 31] Clinical isolates of staphylococci resistant to erythromycin show variable cross resistance with oleandomycin some 30 to 80 per cent of the strains being sensitive to oleandomycin The reasons for these differences in cross resistance between organisms isolated from clinical material and those made resistant in vitro are not known

When erythromycin was first introduced no strains of staphylococci were resistant to it After its use for two years at one institution the incidence of resistant strains was 10 per cent [9] and now four years later it is about 30 per cent [30] Apparently the incidence is related to the extent to which the antibiotic is used

Organisms may rapidly develop resistance to erythromycin in vivo [4, 13] even as early as 48 to 72 hours after therapy has been started [15] Inasmuch as the emergence of erythromycin resistant organisms may be delayed and depressed with combinations of antibiotics it has been suggested that erythromycin be given in combination with other antibiotics for the control of staphylococcal infections [1, 3]

TABLE I

Serum Levels of Erythromycin (μg /ml) after Four Oral Doses of Erythromycin Base and Four of Monopropionyl Ester of Erythromycin

Subject	Propionyl erythromycin	Erythromycin base
Propionyl Erythromycin Given First		
1	11 5	6 0
2	8 0	7 3
3	8 0	1 5
4 *	7 1	6 1
5	6 7	4 5
6	6 1	3 8
7	6 1	1 2
8	5 9	5 7
9	5 1	4 3
10	4 6	2 2
Erythromycin Base Given First		
11	9 9	2 2
12	6 8	8 2
13	6 7	6 9
14 *	6 4	6 5
15 †	5 9	4 2
16 †	5 3	3 0
17	4 6	8 5
18 †	4 5	2 7
19	2 4	0 8
20 †	0 5	5 4
Average	6 1 ‡	4 5
Range	0 5 to 11 5	0 8 to 8 5

Midnight dose of antibiotic taken after light hospital snack but 6 A M dose taken on empty stomach

† Both midnight and 6 A M doses taken with food

‡ Difference between mean levels is 1 6 (6 1 − 4 5) and standard error of difference is 0 75 yielding $t = 2\ 1$ Difference is significant at level of 0 05

actual therapy of infections for a period of five to seven days average levels of 6+ μg /ml of serum were obtained from day to day when multiple assays were performed In one instance the serum level went as high as 16 μg /ml Since staphylococci sensitive to erythromycin are usually inhibited by less than 1 μg /ml it appears that effective serum levels are obtained with the propionyl ester

None of the 3 patients given multiple doses of 500 mg of the ester had gastrointestinal distress In the crossover studies with 20 normal subjects given only four doses of 500 mg each approximately half the subjects had mild gastrointestinal distress with either erythromycin preparation These symptoms consisted of epigastric aching or burning or gnawing hunger sensations

1 Gm every three hours can be given by vein for a total daily dosage of 8 Gm with minimal adverse side effects[1] This may enable one to achieve cures that otherwise might not be possible with oral therapy alone Information is given elsewhere[5 17] on the serum levels of erythromycin that are obtained with the various dosages employed for parenteral administration Only rarely do we now perform serum assays at the Mayo Clinic for erythromycin In serious staphylococcal infections when erythromycin may be employed in combination with another antibiotic we perform a serum bactericidal test utilizing the patient s organism to check on the efficacy of the treatment program[7]

MONOPROPIONYL ERYTHROMYCIN

Recently the monopropionyl ester of erythromycin has become available for study It has been stated that the antibiotic content of the serum is about twice as high when multiple doses of this agent are used as when enteric coated erythromycin base is used[1] and that the antibacterial effect of the serum is greater when the ester is used[1 3]

Crossover studies employing four doses each of the monopropionyl derivative in gelatin capsules and the commercially available enteric coated erythromycin base in tablets were carried out in 20 healthy young men All 20 subjects had not taken any antibiotics previously All had normal renal function They were placed in two groups of 10 each One group was given the tablets of erythromycin base and the other the capsules of erythromycin ester in a dosage of 500 mg every six hours at 12 noon 6 P M 12 midnight and 6 A M A blood sample was drawn at 8 A M two hours after the last of the four doses Thirty hours later the procedure was repeated with the groups reversed In almost all instances the midnight and 6 A M doses were taken on an empty stomach except as indicated in table I The serum samples were stored in the frozen state until all had been collected The assays for erythromycin were carried out by F D Heilman and his assistants by the cup plate method using *Sarcina lutea* as the test organism[2]

The average level obtained two hours after the last dose was 4 5 μg /ml of serum for the erythromycin base and 5 6 μg /ml for the propionyl derivative (table I) In about a third of the subjects the levels of propionyl erythromycin were approximately double or more than double those of the erythromycin base The antibacterial effects of the serum were not determined in this series as was done by Griffith[1] and by Kunin and colleagues[23]

Inasmuch as the propionyl ester gives higher serum levels and greater antibacterial effect than does the erythromycin base in the enteric-coated tablets the propionyl ester will probably replace the tablets currently in use In 3 patients given the ester in a dosage of 500 mg every six hours in the

is required for staphylococcal infections such as upper respiratory infections pneumonia empyema and abscess formation after surgical drainage simple bacteremia without bacterial endocarditis ileocolitis or simple infections of the urinary tract erythromycin alone in full daily dosage or in combination may be highly effective

Erythromycin in combination with streptomycin or bacitracin may be used in the treatment of nonhemolytic streptococcal endocarditis when the patient is allergic to penicillin[39] Similarly in patients with pneumococcal pneumonia or with sore throat caused by β hemolytic streptococci who cannot take penicillin it may be used effectively and is said to be only slightly less effective than penicillin[15] *The treatment of serious staphylococcal infections such as* bacterial endocarditis requires a bactericidal effect[10]

For staphylococcal endocarditis osteomyelitis meningitis and pyelonephritis caused by organisms sensitive to erythromycin this drug must be given in combination with another agent such as bacitracin or streptomycin in order *to delay and suppress the emergence of resistant organisms and to attempt to* provide a bactericidal effect Whether or not the latter has been achieved can be determined by the serum bactericidal test If no bactericidal effect can be achieved with the combination one should alter the treatment regimen and use an antibiotic that is bactericidal for the staphylococcal strain involved such as vancomycin[9, 10] Occasionally if the *Staphylococcus* or another organism is markedly sensitive to erythromycin and only very small amounts are required to kill the organism one may use erythromycin alone to obtain a cure as was obtained by Davis and Romansky[7] in a case of gonococcal endocarditis Except in rare instances erythromycin should not be used alone or even in combination for the treatment of staphylococcal endocarditis[11] which can now be treated effectively with vancomycin if the organism is penicillin resistant

The ideal antistaphylococcal antibiotic should have the following properties it should be bactericidal in small amounts it should not cause irritation when given by mouth or reactions when given parenterally it should be nontoxic to any of the body systems and it should have good penetrative power and should induce little or no resistance in the organisms exposed to it On the basis of these criteria then erythromycin is not the ideal antistaphylococcal agent Nevertheless it continues to be a useful antibiotic for infections with staphylococci that are sensitive to its action

ADVANTAGES AND DISADVANTAGES OF ERYTHROMYCIN THERAPY

Advantages of erythromycin[5] are as follows (1) it has a fairly wide antibacterial spectrum especially for gram positive organisms (2) there is absen e of cross resistance with other antibiotics except for the *other less*

gaseousness bloating or fullness some looseness of the stools or nausea One normal subject had some lower abdominal cramping with diarrhea after the fourth dose of the propionyl ester but was able to continue with the study Two other subjects had to discontinue taking the ester after the second and third doses respectively because of nausea vomiting, and diarrhea in 1 and nausea vomiting and substernal pain apparently from esophageal spasm in the other they had to be excluded in the crossover studies In the treatment of staphylococcal infections with erythromycin I have always started with an oral dosage of 500 mg every six hours and then have reduced the dosage to 400 or 300 mg every 6 hours if any gastrointestinal distress has occurred If the oral dosage of erythromycin needs to be reduced to less than 400 mg, then the drug should be given also intramuscularly or intravenously to supplement oral therapy and to achieve effective serum levels

ABSORPTION AND TOXICITY OF ERYTHROMYCIN

Erythromycin is readily absorbed from the upper part of the gastrointestinal tract It diffuses freely into the various body tissues and cavities[16] and across the mucous membranes of the tracheobronchial tree [5] However it does not cross uninflamed meninges into the cerebrospinal fluid [16] With the usual oral dosages of erythromycin only amounts that are bacteriostatic for staphylococci are found in the serum tissues and body cavities Intravenous injection of 0 5 to 1 Gm rapidly for a 5 to 10 minute period at intervals of three to four hours may give extremely high serum levels and produce a bactericidal effect

Erythromycin is relatively nontoxic Multiple oral dosages of 500 mg every six hours frequently cause gastrointestinal irritation and distress while oral dosages of 300 to 400 mg every six hours seldom do Very little other toxicity has been noted with erythromycin My colleagues and I have not seen any skin reactions drug fever or other allergic manifestations or other evidence of toxicity However urticaria is said to occur rarely [37] Even with large dosages given intravenously such as 1 Gm every three to four hours few adverse effects have been noted

INDICATIONS FOR ERYTHROMYCIN THERAPY

Erythromycin is of value for mild or moderately severe infections caused by staphylococci sensitive to its action but resistant to other antibiotics It is of little or no value when used alone for infections requiring a bactericidal effect such as endocarditis [11] osteomyelitis meningitis and pyelonephritis In these infections it should not be used alone unless it can be demonstrated that such use will give a bactericidal effect When only a bacteriostatic effect

6 GARROD L P The erythromycin group of antibiotics Brit M J 2 57–63 July 13 1957
7 GERACI J E Further experiences with short term (2 weeks) combined penicillin streptomycin therapy for bacterial endocarditis caused by penicillin sensitive streptococci Proc Staff Meet Mayo Clin 30 192–200 May 4 1955
8 GERACI J E AND HEILMAN F R Unpublished data
9 GERACI J E HEILMAN F R NICHOLS D R AND WELLMAN W E Antibiotic therapy of bacterial endocarditis VII Vancomycin for acute micrococcal endocarditis preliminary report Proc Staff Meet Mayo Clin 33 172–181 April 2 1958
10 GERACI J E HEILMAN F R NICHOLS D R WELLMAN W E AND ROSS G T Some laboratory and clinical experiences with a new antibiotic vancomycin Proc Staff Meet Mayo Clin 31 564–582 Oct 17 1956
11 GERACI J E AND MARTIN W J Antibiotic therapy of bacterial endocarditis V Therapeutic considerations of erythromycin Proc Staff Meet Mayo Clin 29 109–118 Feb 24 1954
12 GRIFFITH R S Laboratory and clinical studies with erythromycin propionate *In* Antibiotics Annual 1958–1959 New York, Medical Encyclopedia Inc 1959 pp 364–374
13 HAIGHT T H AND FINLAND M Laboratory and clinical studies on erythromycin New England J Med 247 227–232 Aug. 14 1952
14 HAIGHT T H AND FINLAND M Observations on mode of action of erythromycin Proc Soc Exper Biol & Med 81 188–193 Oct 1952
15 HAIGHT T H ZIEGRA S R AND KAHN F H Erythromycin therapy of respiratory infections II Effects of varying durations of therapy of streptococcal infections on eradication of streptococci and on formation of antistreptolysin O Antib & Chemo 4 439–450 April 1954
16 HEILMAN F R HERRELL W E WELLMAN W E AND GERACI J E Some laboratory and clinical observations on a new antibiotic erythromycin (Ilotycin) Proc Staff Meet Mayo Clin 27 285–304 July 16 1952
17 HERRELL W E Erythromycin New York Medical Encyclopedia Inc 1955 56 pp
18 HERRELL W E NICHOLS D R AND MARTIN W J Erythromycin for infections due to Micrococcus pyogenes J A M A 152 1601–1606 Aug 22 1953
19 JAWETZ E GUNNISON J B COLEMAN V R AND KEMPE H C A laboratory test for bacterial sensitivity to combinations of antibiotics Am J Clin Path 25 1016–1031 Sept 1955
20 JONES W F JR AND FINLAND M Antibiotic combinations antistreptococcal and antistaphylococcal activity of plasma of normal subjects after ingestion of erythromycin or penicillin or both New England J Med 255 1019–1024 Nov 29 1956
21 JONES W F JR NICHOLS R L AND FINLAND M Development of resistance and cross resistance in vitro to erythromycin carbomycin spiramycin oleandomycin and streptogramin Proc Soc Exper Biol & Med 93 388–393 Nov 1956
22 KIRSHBAUM A BOWMAN F W WINTERMERE D M AND FRIEDMAN E R A cup-plate method for the determination of erythromycin concentrations in serum and other body fluids Antib & Chemo 3 537–539 May 1953
23 KUNIN C M PRYLES C V AND FINLAND M Antibacterial activity of serum after oral doses of triacetyloleandomycin erythromycin potassium penicillin V and penicillin V Pediatrics 22 422–431 Sept 1958
24 LEVINE E R AND FROMAN A The efficacy of erythromycin in respiratory infections *In* Antibiotics Annual 1956–1957 New York Medical Encyclopedia Inc pp 1019–1025
25 LOPEZ BELIO M TAKIMURA Y FORNATTO E J AND HOLINGER, P H Erythromycin in the bronchial tree after oral intravenous and aerosol administration *In* Antibiotics Annual 1956–1957 New York, Medical Encyclopedia Inc 1957 pp 152–158
26 LOPEZ BELIO M TAKIMURA Y FOX R T AND LEES W M Clinical and laboratory experiences with erythromycin in treatment of thoracic empyema *In* Antibiotics Annual 1955–1956 New York Medical Encyclopedia Inc 1956 pp 39–47
27 MCGUIRE J M BUNCH R L ANDERSON R C BOAZ H E FLYNN E H POWELL H M AND SMITH J W Ilotycin a new antibiotic Antib & Chemo 2 281–283 June 1952

effective erythromycin like antibiotics such as carbomycin spiramycin, and oleandomycin, (3) it can be taken orally and is fairly well tolerated, when supplemented by parenteral administration particularly intravenous administration high serum levels can be achieved, when given in combination with bacitracin streptomycin, or another bactericidal agent enhanced or synergistic bactericidal effects can be obtained with many strains of staphylococci (4) it has little toxicity and (5) it changes only slightly the flora of the gastrointestinal tract so that superinfection with *Candida* and *Staphylococcus* does not occur

The chief disadvantage of erythromycin is that it is not bactericidal in small amounts In most instances bactericidal levels in the serum cannot be attained for most strains of staphylococci with oral dosage alone In addition it must be given in combination with another antibiotic in an attempt to delay and suppress the emergence of resistant organisms Finally when multiple oral doses of 0 5 Gm are given for a long period significant numbers of patients have gastrointestinal symptoms

The ideal antistaphylococcal agent has not appeared at the time of this writing However with the introduction of the newer bactericidal antistaphylococcal agents such as vancomycin ristocetin and kanamycin which require parenteral administration the ability to handle infections caused by staphylococci resistant to penicillin and the more commonly used antibiotics seems to be considerably improved The relative position and effectiveness of erythromycin in the imposing list of antistaphylococcal agents now available to the clinician remain to be ascertained

ACKNOWLEDGMENT

Erythromycin propionate was supplied by R S Griffith of Eli Lilly & Co Indianapolis Indiana

I am indebted to Dr D R Holsinger for his help in carrying out the studies tabulated in table I

BIBLIOGRAPHY

1 ANON Erythromycin resistant staphylococci (editorial) New England J Med *251* 491 Sept. 16 *1956*

2 COLEMAN V R GUNNISON J B AND JAWETZ E Participation of erythromycin and carbomycin in combined antibiotic action *in vitro* Proc Soc Exper Biol & Med *83* 668 670 Aug-Sept 1953

3 DAVIS D S AND ROMANSKY M J Successful treatment of gonococcic endocarditis with erythromycin review of the literature Am J Med *21* 473-480 Sept 1956

4 FINLAND M Emergence of antibiotic resistant bacteria New England J Med *253* 909-922 969-979 1955

5 FORFAR J O., AND MACCABE A F Erythromycin a review Antibiotica et chemotherapia *4* 115-157 *1957*

Chapter III

Oleandomycin—Its Derivatives and Combinations—in the Treatment of Staphylococcal Infections

E L Foltz
Assistant Professor of Medicine The School of Medicine
University of Pennsylvania Philadelphia Pa

The search for an antimicrobial agent effective against staphylococci has been spurred on by the ability of this organism to emerge resistant to every antibiotic substance that has proved clinically useful The introduction of oleandomycin in 1954 provided the clinician with an intermediate spectrum antibiotic that was effective against the staphylococci as well as most gram positive organisms and a few gram negative bacteria Since the first report of its characteristics it has been used widely in many different infectious diseases the salts and esters of oleandomycin have been produced and employed in the management of staphylococcal disease The development of chemical and physical combinations with other antibiotics has led also to a clinical trial of these agents in the management of staphylococcal disease

Oleandomycin (Matromycin and Romicil*) was first described by Sobin et al[13] and designated PA 105 This basic antibiotic material was found to be elaborated by a strain of *Streptomyces antibioticus* when grown under suitable aerobic conditions in organic media The material was recovered and purified through a series of steps including filtration and extraction of the filtrate with various organic solvents under suitable *p*H conditions the compound was recovered as the crystalline hydrated hydrochloride of oleandomycin

Oleandomycin was found to be effective by in vitro tests against the gram positive organisms such as staphylococci streptococci pneumococci the spore forming bacilli the anaerobic clostridia *Listeria* and *Erysipelothrix* a

* The trade name of Chas Pfizer & Co for oleandomycin is Matromycin of Hoffmann LaRoche is Romicil

28 MANTEN A Synergism and antagonism between antibiotic mixtures containing erythromycin Antib & Chemo *4* 1228–1233 Dec 1954
29 MARTIN W J NICHOLS D R WELLMAN W E AND GERACI J E Changes in sensitivity of Micrococcus pyogenes to erythromycin over a period of 2 years Proc Staff Meet Mayo Clin *29* 379–387 June 30 1954
30 NEEDHAM G Unpublished data
31 NEEDHAM G M AND GERACI J E Laboratory studies of oleandomycin (Matromycin) AM&CT *3* 334–335 Oct 1956
32 PETERSDORF R G BENNETT I L JR AND ROSE M C The sensitivity of pathogenic bacteria to a series of antibiotics Bull Johns Hopkins Hosp *100* 1–13 Jan 1957
33 RANTZ L A AND RANDALL E Antibiotic synergism and *Staphylococcus aureus* Antib & Chemo *2* 645–652 Dec 1952
34 REISCH A L MARTIN W J NICHOLS D R AND HEILMAN F R Triacetyl oleandomycin and erythromycin in serum comparison of concentrations and of antibacterial effects Proc Staff Meet Mayo Clin *33* 187–193 April 16 1958
35 ROMANSKY M J NASOU J P DAVIS D S AND RITTS R E JR The treatment of one hundred and seventy-one patients with erythromycin including one hundred and thirty two with bacterial pneumonia *In* Antibiotics Annual 1955–1956 New York Medical Encyclopedia Inc 1956 pp 48–62
36 UNGER L AND KISCH A Observations on bacteriostatic and bactericidal action of erythromycin Proc Soc Exper Biol & Med *98* 176–178 May 1958
37 WELCH H LEWIS C N WEINSTEIN H I AND BOECKMAN B B Severe reactions to antibiotics a nationwide survey *In* Antibiotics Annual 1957–1958 New York Medical Encyclopedia Inc 1958 pp 296–309
38 WILEY P F GERZON K FLYNN E H SIGAL M V JR WEAVER O QUARCK U C CHAUVETTE R R AND MONOHAN R Erythromycin X structure of erythromycin J Am Chem Soc *79* 6062–6070 Nov 20 1957
39 YOW E M Problems encountered in the management of endocarditis South M J *50* 987–991 Aug 1957

PHYSICAL AND CHEMICAL CHARACTERISTICS OF OLEANDOMYCIN AND ITS DERIVATIVES

Originally oleandomycin was obtained as the hydrated crystalline hydro chloride salt Oleandomycin was shown to be a weak base with a chemical formula of $C_3 H_{61}NO_1$ This compound consisted of two sugars L oleandrose and desosamine bound in glycosidic linkage to a large complex lactone nucleus which was designated an oleandolide Oleandomycin was therefore classified as a member of the macrolide group of antibiotics Oleandomycin appears as a colorless prism

Melting Point The melting point of the various derivatives of oleandomycin and the base itself are shown in table I The base shows the lowest melting point at 110 C with higher values noted for each of the salts or derivatives Triacetyloleandomycin has one of the highest melting points (176 C) of any of the derivatives described to the present time

Optical Activity The optical rotatory effects in methanol have been de scribed as levorotatory for all of the salts and derivatives of oleandomycin as well as the base with the exception of the penicillin salt of oleandomycin This material has been shown to be dextrorotatory Positive rotatory dispersion Cotton effect has permitted the detection of an acyl substituent on the olean dolide moiety when studied at 325 mμ [4]

Solubility The solubility of the original oleandomycin hydrochloride was found to be greater than 100 Gm /100 ml of water Oleandomycin base has a much lower degree of solubility—0 5 Gm /100 ml of water Oleandomycin is relatively highly soluble in alkaline aqueous solutions which differentiated this material from carbomycin and erythromycin The base was also shown to be quite soluble in organic solvent solutions

Triacetyloleandomycin is relatively insoluble in water (less than 0 1 Gm / 100 ml of water) It was also noted to be relatively insoluble in buffered aqueous solutions with a pH range of 4 to 7 Oleandopen shows a solubility of 0 5 Gm /100 ml of water under the usual laboratory conditions but maxi mum solubility has been described at approximately 1 5 Gm /100 ml of water [69]

Stability A relatively high degree of stability has been ascribed to the oleandomycin salts [5] The original hydrated hydrochloride could be rendered as an anhydrous hydrochloride by drying for 18 hours at 100 C in vacuo no loss in antibiotic activity was noted after such treatment No loss of antimi crobial activity was described when 0 1 per cent aqueous solutions of the hydrochloride were permitted to stand 24 hours at room temperature in buffered solutions at pH 2 2 5 7 and 9 Sous and co workers[137] subjected solutions containing 100 μg /ml to temperatures of 120 C by autoclaving for 30 minutes they noted an approximate reduction of 80 per cent in antimi

few gram negative organisms including strains of *Neisseria Hemophilus* and *Brucella* were also found to be susceptible to its action Certain mycobacteria rickettsiae and larger viruses have been considered to be inhibited by its action It was found to be ineffective against most of the enteric bacteria except in extremely high concentrations which were not obtainable in vivo except in the urine Its bacterial spectrum was closely comparable therefore to that described in previous years for erythromycin

During the course of the next two years (1954–1956), a few papers appeared describing the antimicrobial activity as well as some preliminary clinical trials Before clinical evaluation had reached the point where effectiveness could be established a major controversy arose when the clinical use of this drug in combination with tetracycline was recommended on the basis of in vitro studies that suggested an enhanced antibacterial activity of these agents [40]

In 1956 oleandopen the oleandomycin salt of penicillin G was introduced The antimicrobial action of oleandopen and its pharmacological characteristics were published by Hobby and her co workers [60] The clinical results after oleandopen therapy in 7 patients were also described [108] but there have been no additional reports of its clinical effectiveness and the studies on the salt have not been pursued

In 1957 Celmer et al [5] announced the preparation of several oleandomycin derivatives These derivatives were obtained as part of an intentional study aimed at improving the chemical pharmaceutical and therapeutic effectiveness of oleandomycin One of these derivatives triacetyloleandomycin (Cyclamycin Tao*) was found to give superior pharmacological results as noted by higher serum concentrations and lower ED_{50} when compared with oleandomycin and other intermediate spectrum antibiotics Several papers have appeared since its introduction which have described its clinical and bacteriological activity

In 1958 all of the theoretically possible partially acetylated derivatives as well as the homologous tripropionyl and tributyryl derivatives of oleandomycin were described by Celmer and Hochstein [6] The higher serum concentrations noted for triacetyloleandomycin were shared by 1 monoacetyl 1 2-diacetyl 1 3 diacetyl and tripropionyl oleandomycin Clinical trials have not been reported for these agents

Oleandomycin and more recently triacetyloleandomycin provide additional antimicrobial weapons in the continuing fight against infections due to staphylococci as well as other organisms It is important to review the evidence of the effectiveness of these agents by considering the chemical antibacterial and pharmacological properties as well as the clinical results these facets will be considered separately in this review

* The trade name of Wyeth Laboratories for triacetyloleandomycin is Cyclamycin of J B Roerig & Co Division Chas Pfizer & Co is Tao

TABLE II

Papergram Migrations [5]

	R	Ro *
Oleandomycin	0 50	0 4
Oleandomycin hydrochloride	0 50	0 4
Oleandomycin phosphate	0 50	0 4
Oleandomycin chlorohydrin hydrochloride	0 50	0 3
Triacetyloleandomycin	0 95	—

$$* \text{Ro} = \frac{\text{distance of spot from origin}}{\text{distance from origin to end of paper}} \text{(16 hours development)}$$

crobial activity These workers also demonstrated a loss of antimicrobial potency of approximately 20 per cent when a similar solution was exposed at *p*H 2 for five hours relatively high stability was noted for oleandomycin at *p*H 9

Triacetyloleandomycin is relatively stable aqueous solutions (50 mg /ml at *p*H 2 5) were kept at temperatures of 25 and 37 C with no loss of potency or change in chemical composition Similar solutions of oleandomycin phosphate showed no appreciable change at 25 C but a 25 per cent loss of antimicrobial potency was noted when the solution was kept at a temperature of 37 C [4] A solution of oleandomycin at *p*H 9 0 lost approximately 50 per cent of its potency after three weeks at 25 C a similar solution of 3 monoacetyloleandomycin showed less than a 10 per cent loss of antimicrobial potency under similar conditions Oleandomycin chlorohydrin hydrochloride is a relatively unstable compound and tends to revert to oleandomycin The chloroform solvate of oleandomycin base has been shown to be relatively stable the chemical composition of a laboratory sample has remained constant over a period of two years

Chromatographic Properties Oleandomycin is distinct and different from erythromycin chromatographically Papergram migrations have permitted the differentiation of several oleandomycin compounds samples of oleandomycin and triacetyloleandomycin when applied to filter paper strips previously impregnated with formamide and utilizing a benzene system were separated after 16 hours of development The R_f values are listed in table II A minor antibiotic component that had been noted in fermentation broths and subsequent recoveries was found to have the same papergram migration as oleandomycin chlorohydrate

Countercurrent distribution studies were performed [5] utilizing the system of Pettinga distribution coefficients (23) were obtained for oleandomycin (K = 0 5) oleandomycin chlorohydrin (K = 2 3) and the minor antibiotic component (K = 2 3)

TABLE I

Physical and Chemical Properties of Oleandomycin Base and Derivatives

	Appearance	Melting point degrees C	Optical rotation degrees	Water solubility Gm /100 ml	pKá	Chemical formula
Oleandomycin (base)	Colorless pr *	110	−65	0 5	8 5	C35H NO
Oleandomycin chloroform solvate	Colorless pr	122	−55	0 5	8 5	C36H[illegible]NO Cl
Oleandomycin hydrochloride	Colorless ne †	135	−57	100	8 5	C35H NO Cl
Oleandomycin phosphate	Colorless ne	150	−52	100	8 5	C35H NO P
Oleandopen	Colorless ne	140	+63	0 5–1 5	8 5	C[illegible]H N O S
Oleandomycin chlorohydrin hydrochloride	Colorless ne	152	−79	100	8 5	C35H[illegible]NO Cl
Triacetyloleandomycin	Colorless ne	176	−23	0 1	6 6	C H[illegible]NO
2 3-diacetyloleandomycin	Colorless pr	182	−24	0 5	7 7	C38H[illegible]NO
1 3-diacetyloleandomycin	Colorless pr	162	−24	0 5	6 6	C38H[illegible]NO
1 [illegible]-diacetyloleandomycin	Colorless am ‡	100	−59	0 5	6 6	C38H[illegible]NO
3 monoacetyloleandomycin	Colorless pr	182	−25	0 5	8 0	C37H[illegible]NO
[illegible] monoacetyloleandomycin	Colorless am	100	−63	0 5	8 0	C37H[illegible]NO[illegible]
1 monoacetyloleandomycin	Colorless am	100	−62	0 5	6 7	C37H[illegible]NO
Tripropionyloleandomycin	Colorless ne	158	−22	0 1	6 6	C H NO
Tributyryloleandomycin	Colorless pr	114	−21	0 1	6 6	C H[illegible]NO

* pr = prism
† *ne* = *needle*
‡ am = amorphous

TABLE II

Papergram Migrations

	R	Ro *
Oleandomycin	0 50	0 4
Oleandomycin hydrochloride	0 50	0 4
Oleandomycin phosphate	0 50	0 4
Oleandomycin chlorohydrin hydrochloride	0 50	0 3
Triacetyloleandomycin	0 95	—

$$* \text{Ro} = \frac{\text{distance of spot from origin}}{\text{distance from origin to end of paper}} \text{(16 hours development)}$$

crobial activity These workers also demonstrated a loss of antimicrobial potency of approximately 20 per cent when a similar solution was exposed at *p*H 2 for five hours relatively high stability was noted for oleandomycin at *p*H 9

Triacetyloleandomycin is relatively stable aqueous solutions (50 mg /ml at *p*H 2 5) were kept at temperatures of 25 and 37 C with no loss of potency or change in chemical composition Similar solutions of oleandomycin phosphate showed no appreciable change at 25 C but a 25 per cent loss of antimicrobial potency was noted when the solution was kept at a temperature of 37 C [4] A solution of oleandomycin at *p*H 9 0 lost approximately 50 per cent of its potency after three weeks at 25 C a similar solution of 3 monoacetyloleandomycin showed less than a 10 per cent loss of antimicrobial potency under similar conditions Oleandomycin chlorohydrin hydrochloride is a relatively unstable compound and tends to revert to oleandomycin The chloroform solvate of oleandomycin base has been shown to be relatively stable the chemical composition of a laboratory sample has remained constant over a period of two years

Chromatographic Properties Oleandomycin is distinct and different from erythromycin chromatographically Papergram migrations have permitted the differentiation of several oleandomycin compounds samples of oleandomycin and triacetyloleandomycin when applied to filter paper strips previously impregnated with formamide and utilizing a benzene system were separated after 16 hours of development The R_f values are listed in table II A minor antibiotic component that had been noted in fermentation broths and subsequent recoveries was found to have the same papergram migration as oleandomycin chlorohydrate

Countercurrent distribution studies were performed utilizing the system of Pettinga distribution coefficients (23) were obtained for oleandomycin (K = 0 5) oleandomycin chlorohydrin (K = 2 3) and the minor antibiotic component (K = 2 3)

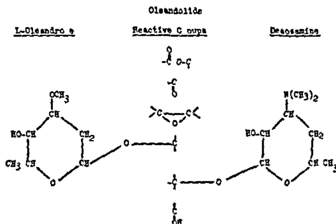


FIG 1 Oleandomycin moieties Reproduced with permission from Celmer et al Antibiotics Annual 1957–1958 New York Medical Encyclopedia Inc 1958 p 477

Potentiometry Oleandomycin was originally described as a relatively weak base a 1 1 ethanol water solution on potentiometric titration resulted in a pKa value of 8 5 A similar value was obtained for oleandomycin chlorohydrin under similar conditions Triacetyloleandomycin was found to be less basic with a pKa value of 6 6 this decrease in basic properties has been ascribed to the substitution of hydroxyl substituents on the desosamine moiety [36] Similar lowering of basicity has been noted for the derivatives 1 monoacetyl 1 2 diacetyl 1 3 diacetyl and tripropionyl oleandomycin which also contain an acyl substituent on the desosamine moiety

Chemical Structure Original studies with PA 105 suggested an empirical formula approximating $C_{37}H_{67}NO_{13}$ HCl Subsequent studies of oleandomycin samples suggested a composition for the base of $C_{35}H_{61-63}NO_{1}$ The presently accepted structural findings have resulted in a specific formulation of $C_{35}H_{61}NO_{1}$ This compound was shown to consist of two sugars L oleandrose and desosamine which were bound in a glycosidic linkage to an oleandolide nucleus (fig 1) degradation reactions which destroyed the lactone or sugar linkages were accompanied by a loss in antibacterial activity An antibiotically active derivative oleandomycin chlorohydrin hydrochloride resulted from the addition of two equivalents of anhydrous hydrogen chloride to an ethylacetate solution of oleandomycin

Triacetyloleandomycin was prepared by complete acylation of the hydroxyl groups of which there is one in each of the three chemical moieties of oleandomycin Because of the difference in reaction rates at the different sites of acylation the partial acetyl esters could be formed initially on the desosamine moiety (1 monoacetyl-oleandomycin) and second on the L-oleandrose moiety (1 2-diacetyl oleandomycin)

In 1958 Celmer and Hochstein [6] described all the theoretically possible partially acetylated derivatives as well as the homologous tripropionyl and

tributyryl derivatives of oleandomycin Interesting correlations among these compounds were noted Triacetyloleandomycin as well as 1 monoacetyl 1 2-diacetyl 1 3 diacetyl and tripropionyl-oleandomycin were noted to give higher serum concentrations when administered orally tributyryloleandomycin was a notable exception in this characteristic All of these compounds contain an acyl substituent on the desosamine moiety which lowers the basicity The derivatives that contain an acyl substituent on the oleandrose moiety exhibited lower in vitro activity however in vivo effects did not suggest that these compounds were less active [4]

Deacetylation by saponification or methanolysis was responsible for re moval of the acetyl groups in the same order as they were introduced By using methanolysis under alkaline catalysis the deacetylation sequence fol lowed the pattern of L-oleandrose before the desosamine the third acetyl substituent remaining on the oleandolide was extremely difficult to remove by chemical means and formed a very stable compound as well as retaining high biological potency

Elemental analysis of oleandomycin indicated the chemical formula to be as previously described $C_3 H_{61}NO_1$ the analytical data (carbon 61 20 hydrogen 8 88 nitrogen 2 27 molecular weight 690) were found to com pare closely with calculated weight values (carbon 61 1 hydrogen 8 94 nitrogen 2 04 molecular weight 688)

Infrared Absorption The infrared absorption spectra have been described by Sobin et al[135] and by Celmer et al When the spectra of these compounds were determined in potassium bromide pellets they showed characteristic absorption peaks around 3 3 4 and 5 8 μ with a band of absorption of irregu lar intensity from 6 6 to 11 0 Triacetyloleandomycin did not show the char acteristic absorption peak in the vicinity of 3 0 μ and this is associated with the lack of free hydroxyl groups The curves are reproduced in figures 2 and 3

Ultraviolet Absorption Oleandomycin triacetyloleandomycin oleando mycin salts and other derivatives of oleandomycin already described charac teristically exhibit a low intensity ultraviolet absorption with a broad maximum near 290 mμ E_1^{1cm} 0 5 to 0 9

Like many other antimicrobials oleandomycin possesses the ability to bind with serum proteins and other biological fluids This binding is apparently reversible The protein binding effects are primarily important in relation to a reduction of the antimicrobial activity This will be discussed in a later section

ANTIMICROBIAL ACTIVITY

In Vitro Results ANTIBACTERIAL SPECTRUM The range of antibacterial activity of oleandomycin was first described by Sobin et al[135] in 1954 they

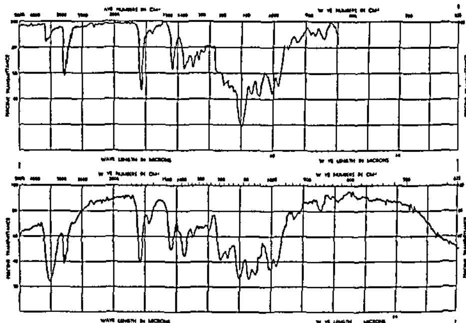


FIG 2 Upper curve P A 105 in chloroform solution Lower curve P A 105 hydrochloride in a potassium bromide pellet Reproduced with permission from Sobin et al Antibiotics Annual 1954–1955 New York Medical Encyclopedia Inc 1955 p 827

demonstrated that it was effective against many gram positive species of bacteria including streptococci pneumococci staphylococci the large aerobic spore forming bacilli the anaerobic clostridia the corynebacteria *Listeria monocytogenes* and *Erysipelothrix rhusopathiae* in addition gram negative organisms of the genera *Hemophilus Brucella* and *Neisseria* were found to be inhibited by oleandomycin Some activity was also noted against certain mycobacteria The large majority of gram negative organisms including the *Enterobacteriaceae* were not affected by this antimicrobial agent

Since the initial report other groups including Fust et al [55] Gagliardi [56] Andrieu et al [2] Haukenes and Tonder [67] Reedy and Shaffer [114] Hobby et al [69] and Sous et al [137] have contributed information as to the susceptibility of a large number of organisms to oleandomycin nearly all the workers have substantiated the original findings of Sobin et al and have extended the observations [137] as to the insusceptibility of fungi to this antibiotic agent The ranges of effective antibacterial concentrations found by the various groups for the species tested are shown in table III

Leming and Flanigan[97] reported recently on a large survey of antimicrobial activity by the disc plate method in their study oleandomycin discs of 15 μg concentration were used to determine the susceptibility of 1725 different

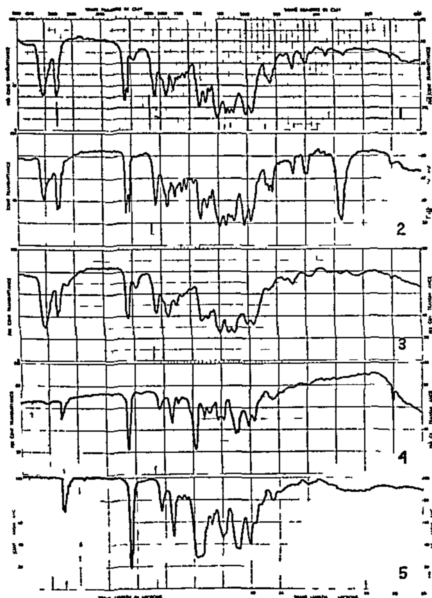


FIG 3 Infrared absorption spectra determined in potassium bromide pellets are shown 1 Oleandomycin base 2 oleandomycin base chloroform solvate 3 oleandomycin chlorohydrin hydrochloride 4 triacetyloleandomycin Spectrum determined in chloroform solution is also given 5 triacetyloleandomycin Reproduced with permission from Celmer et al Antibiotics Annual 1957–1958 New York Medical Encyclopedia, Inc 1958 p 481

TABLE III

In Vitro Susceptibility of
(Inhibitory Concentrations Expressed

	Sobin et al [135]		Fust et al [55]			Andrieu et al [4]	
	No *	Range	No	Range	Gagliardi [58]	No	Range
M pyogenes var *aureus*	25	<0 19–3 12	44	<0 37–3 0	0 19–3 90	126	0 2–>100
M pyogenes var *albus*	1		9	<0 156–2 5	0 78		
S lutea			1	0 156			
Micrococcus species							
Str pyogenes A	1	0 78	24	<0 09–3 0	0 05–1 60	3	0 20–0 40
Str pyogenes B							
Str pyogenes C							
Str faecalis etc D	3	1 56	15	0 312–4 8	1 0–1 56	5	0 80–3 1
Str viridans			35	0 156–1 25	0 25		
Nonhemolytic *Streptococcus*			17	<0 09–2 5		1	0 2
G tetragena							
D pneumoniae	4	<0 19–1 56	8	<0 045–3 0	0 01–3 90	1	<0 2
C diphtheriae	1	1 56	1	0 23	0 05–1 56	1	0 4
L monocytogenes	1	0 78			0 78–3 12	3	3 1
Ery rhusiopathiae	4	<0 19–0 39	1	<0 19	0 19–0 7		
B subtilis	1	0 39			0 39–1 7	1	0 8
B anthracis	1	0 78		0 48	0 7–5 0	1	0 8
B mycoides	1	1 56			1 56		
Bacillus species							
Cl tetani	1	6 25			1 50–6 25		
Cl sporogenes	1	3 12			1 50–3 12		
Cl perfringens					1 50–7 00		
Myco phlei	1	1 56			1 56		
Myco smegmatis	1	1 56					
Myco tuberculosis var *hominis*			2	>100	50 00		
Myco tuberculosis var *bovis*			1	12 5–>100			
Myco tuberculosis							
N catarrhalis	1	3 12			2 50–3 12	2	0 8
N meningitidis	1	1 56			1 56–6 25		
N gonorrhoeae	1	3 12			3 12–6 25		
B bronchoseptica	1	6 25				1	50 0
B abortus						1	0 8
B melitensis						1	0 4
H influen ae	1	0 078			0 078–20 0		
H pertussis					0 2		
H Koch Weeks				11 7			
H duplex							

TABLE III

Microorganisms to Oleandomycin as Oleandomycin μg /ml. of Nutrient)

Haukenes and Tonder [7]		Sous et al [7]		Reedy and Shaffer [114]		Hobby et al [69]	
No	Range	No	Range	No	Range	No	Range
65	0 16–5 0	10	0 78–6 25	10	0 312–1 25	26	0 280–22 5
		2	3 125				
1	0 39						
3	0 076–1 56	5	0 19–1 56	5	0 10–3 12	1	0 07
11	0 31–1 56	5	1 56–3 12	4	0 39–3 12	3	0 14–0 79
3	0 16–0 62					5	0 14–2 25
1	0 78						
3	<0 076–0 39	4	0 19–0 39	5	0 039–0 156	1	0 07
1	<0 076	4	0 024–0 095	4	0 078–0 312		
		3	1 56				
		1	0 045				
		6	0 09–0 39	10	0 39–>100		
		1	>100				
		1	>100				
		2	>100				
		2	>100				

TABLE III

In Vitro Susceptibility of
(Inhibitory Concentrations Expressed

	Sobin et al [135]		Fust et al [55]			Andrieu et al [8]	
	No *	Range	No	Range	Gaghardi [56]	No	Range
M pyogenes var *aureus*	25	<0 19–3 12	44	<0 37–3 0	0 19–3 90	126	0 2–>100
M pyogenes var *albus*	1		9	<0 156–2 5	0 78		
S lutea			1	0 156			
Micrococcus species							
Str pyogenes A	1	0 78	24	<0 09–3 0	0 05–3 60	3	0 20–0 40
Str pyogenes B							
Str pyogenes C							
Str faecalis etc D	3	1 56	15	0 312–4 8	1 0–1 56	5	0 80–3 1
Str viridans			35	0 156–1 25	0 25		
Nonhemolytic *Streptococcus*			17	<0 09–2 5		1	0 2
G tetragena							
D pneumoniae	4	<0 19–1 56	8	<0 045–3 0	0 01–3 90	1	<0 2
C diphtheriae	1	1 56	1	0 23	0 05–1 56	1	0 4
L monocytogenes	1	0 78			0 78–3 12	3	3 1
Ery rhusiopathiae	4	<0 19–0 39	1	<0 19	0 19–0 7		
B subtilis	1	0 39			0 39–1 7	1	0 8
B anthracis	1	0 78		0 48	0 7–5 0	1	0 8
B mycoides	1	1 56			1 56		
Bacillus species							
Cl tetani	1	6 25			1 50–6 25		
Cl sporogenes	1	3 12			1 50–3 12		
Cl perfringens					1 50–7 00		
Myco phlei	1	1 56			1 56		
Myco smegmatis	1	1 56					
Myco tuberculosis var *hominis*			2	>100	50 00		
Myco tuberculosis var *bovis*			1	12 5–>100			
Myco tuberculosis							
N catarrhalis	1	3 12			2 50–3 12	2	0 8
N meningitidis	1	1 56			1 56–6 25		
N gonorrhoeae	1	3 12			3 12–6 25		
B bronchoseptica	1	6 25				1	50 0
B abortus						1	0 8
B melitensis						1	0 4
H influenzae	1	0 078			0 078–20 0		
H pertussis					0 2		
H Koch Weeks				11 7			
H duplex							

TABLE III (*Continued*)

Microorganisms to Oleandomycin
as Oleandomycin, μg./ml of Nutrient)

Haukenes and Tonder		Sous et al [37]		Reedy and Shaffer [114]		Hobby et al [9]	
No	Range	No	Range	No	Range	No	Range
		5	25			1	158
1	>100			10	>100		
1	>100	5	>100	10	>100	1	158
				9	>100		
1 1	>100 >100	5	>100				
		7	>100	6	>100		
						1 1	275 225
		5	>100	6	50->100		
		1 1 1	>100 >100 >100				
		1 1	>100 >100				

3 12 μg /ml Jones and Finland [76] in a study of five new antibiotics tested 74 different strains of hemolytic streptococci other than those of Lancefield group D the majority of these isolates were susceptible to a concentration ranging between 0 8 and 1 6 μg /ml of oleandomycin Groups B and C were apparently more susceptible than groups A and C Enterococci (group D streptococci) were considerably more resistant to the action of oleandomycin and required a concentration between 6 3 and 12 5 μg /ml to inhibit 90 per cent of 70 strains so tested These studies indicate the susceptibility of the majority of streptococci with a possible exception of the enterococci which require for inhibition concentrations somewhat higher than those that can be readily achieved in man by the usual dosages

ANTISTAPHYLOCOCCAL ACTIVITY Since the introduction of this compound for clinical use an increase in the morbidity of staphylococcal infections has

TABLE III (*Continued*)

In Vitro Susceptibility of
(Inhibitory Concentrations Expressed

	Sobin et al [135]		Fust et al [55]		Gagliardi [56]	Andrieu et al [2]	
	No *	Range	No	Range		No	Range
K pneumoniae	1	>100	2	>40		1	>100
A aerogenes	3	>100					
E coli	1	>100	34	>40		2	>100
Proteus species			6	>40		1	>100
P vulgaris	1	>100					
P morgani							
Ps aeruginosa	1	>100	5	>40			
S paratyphi	1	>100				3	>100
S schottmulleri	1	>100					
S typhimurium				>1000		1	>100
S typhosa	1	>100				1	>100
S enteritidis				>1000		1	>100
Salmonella species							
Shigella species				>40			
Sh flexneri						1	>100
Sh sonnei						1	>100
Fungi							
C albicans	1	>100	2	>40			
T mentagrophytes				>1000			
Epiderm K W							
Aspergillus parasites							
S beurmanni							
Yeast							

* No indicates number of organisms tested

gram positive cocci they found that 90 7 per cent of these organisms were susceptible to the oleandomycin in the discs They also presented data on 236 gram negative organisms similarly tested for susceptibility to oleandomycin Three per cent of these organisms were found to be sensitive to the oleando mycin contained in the discs

Since the antibacterial activity of oleandomycin is primarily against the gram positive organisms it was natural that attention would be focused on the susceptibility of streptococci and staphylococci

ACTIVITY AGAINST STREPTOCOCCI Garrod [58] in a study of erythromycin like antibiotics listed six strains of streptococci that were susceptible to a concentration of oleandomycin equal to or less than 0 25 μg /ml Trafton and Lind [141] in a study of oleandomycin in urinary tract infections listed 24 enterococci of which 22 were susceptible to a concentration equal to or less than

number of isolates represented in these papers exceeds 3000 organisms The percentage of susceptible strains varies from a reported low of 31 per cent by Waisbren and Strelitzer[143] to a high of 100 per cent reported by Cimmino et al [23] An unweighted average for this series of reports gives a susceptibility rate of approximately 85 per cent of the staphylococci tested Most of the papers that reported the effectiveness of oleandomycin against staphylococci presented data in such a fashion as to permit the selection of those organisms that were susceptible to a concentration of oleandomycin of 3 1 µg or less per ml of nutrient media since such a concentration in serum can be achieved in vivo this figure of susceptibility might be expected to correlate to some degree with the clinical results

A few of these reports described the use of selected staphylococcal isolates English[37] showed 101 erythromycin resistant isolates in his study of cross resistance Garrod [5] was similarly interested in the problem of erythromycin resistance and selected 45 different strains of which the majority were insensitive to a concentration of erythromycin of 8 µg or greater per ml As will be shown later such selections might well have weighted the data against the effectiveness of oleandomycin since many strains resistant to erythromycin have been shown to be resistant also to oleandomycin Hasenclever[66] was primarily interested in the comparison of oleandomycin and an oleandomycin tetracycline mixture 25 of the 37 isolates used in this study were selected on the basis of being resistant to tetracycline at a concentration of 50 µg or greater per ml while the remaining 12 were selected on the basis of being susceptible to 5 µg or less of tetracycline per ml of media The 65 organisms reported in the study of Oswald and Welch[105] were selected from a group of 202 organisms on the basis that the selected strains demonstrated synergism of action by a mixture of oleandomycin and tetracycline It does not appear that either of the two latter studies weighted the data in favor of oleandomycin on the basis of these selections In many of the other reports included in table IV the authors were primarily concerned with demonstrating cross resistance or enhancement of action between pairs of antibiotics and the data collected on oleandomycin alone were incidental and not the primary reason for the report

MODE OF ACTION Descriptions as to the mode of action of oleandomycin did not appear in the literature until 1957 Andrieu and co-workers first presented data to suggest that oleandomycin could be considered bactericidal for 10 strains of staphylococci and four isolates of enterococci Rantz and co workers[113] presented data on 33 readily susceptible strains of staphylococci in which the minimum inhibitory and minimum bactericidal concentrations were nearly the same they called attention to the fact that viable organisms in small numbers were frequently recovered from tubes that showed no turbidity and that contained the highest concentrations of antibiotic The

TABLE IV

Percentage of Staphylococci Susceptible to Oleandomycin

Authors	No of isolates	% susceptible	Oleandomycin concentration µg /ml
Broth dilution method			
Andrieu et al [2]	126	88	3 1
Bunger and Schutze [20]	61	95	
Cimmino et al [5]	332	100	1
Colville et al [9]	74	89	3 12
Dumas et al [33]	50	86	2 5
Elliott and Hall [35]	30	83	3 12
English [37]	100	74	3 12
Flanigan et al [8]	100	92	3 12
Foltz [49]	50	98	2 5
Foulke and Romansky [51]	103	75	5 0
Fust et al [54]	80	75	3.0
Garrod [58]	45	65	2 0
Hasenclever [66]	37	78	2 5
Jones and Finland [74]	103	87	3 1
Levitt and Hubble [90]	30	73	3 12
McFadden and Schelhart [94]	145	78	3 12
Noyes et al [101]	100	96	2 0
Oswald and Welch [103]	65	99	2 0
Petersdorf et al [109]	200	76	5 0
Rantz et al [113]	41	83	2 5
Ross et al [120]	165	99	3 12
Sobin et al [35]	21	95	3 12
Trafton and Lind [141]	27	89	3 12
Wai bren and Strelitzer [43]	45	31	3 0
Disc plate method			
Haukenes and Tonder [67]	281	88	1
Koch and Lepley [82]	451	89	2
Leming and Flanigan [87]		88	1 5
Rivera et al [117]	143	98	2 0
Method not described			
Esselier and Keith [42]	27	82	
Muth and Weyer [9]		92	
Average		85	

apparently occurred as well as an increase in the number of antibiotic resistant staphylococci It was only natural that a great many workers would test the effectiveness in vitro of oleandomycin against staphylococci Approximately 30 different papers have been published in the past four years delineating the effectiveness of oleandomycin against the staphylococci (see table IV) The majority of these papers reported studies on the minimal inhibitory concentrations of oleandomycin A few papers described the results of susceptibility tests by the disc plate method and two authors did not specify the exact method by which the results were obtained The papers have originated in the United States *Great Britain Germany* Norway France and Italy The total

cocci to antibiotics has occurred with amazing regularity with each new agent shortly after its introduction the isolation of resistant clinical strains and the rate at which resistance is acquired have been the targets of study in the early evaluation of each new antimicrobial agent

In the description of the antimicrobial activity of oleandomycin Sobin et al[135] listed one resistant strain of *M pyogenes* var *aureus* that did not respond to a concentration of oleandomycin in excess of 100 μg/ml this strain had developed resistance to carbomycin and erythromycin in previous laboratory manipulations A subsequent publication from the same laboratory[40] indicated that a significant increase in resistance to oleandomycin could be accomplished by serial transfers of a strain of *Staphylococcus* in the presence of increasing concentrations of oleandomycin under these conditions the minimum inhibitory concentration of the *Staphylococcus aureus* had increased from 0 19 to 100 μg/ml after 19 successive transfers In a similar study *Streptococcus pyogenes* ATCC 8668 showed emergence of resistance an original minimum inhibitory concentration of 0 0625 μg/ml increased to 50 μg/ml after 19 successive transfers

The rate at which emergence of resistance to oleandomycin occurred was compared with that for novobiocin by Noyes et al [101] under the conditions of their experiments oleandomycin showed approximately a sixteenfold increase in resistance after six serial transfers in contrast to a 76 fold increase in resistance to novobiocin This group felt that resistance to oleandomycin occurred in a stepwise fashion Andrieu and co workers described the slow emergence of resistance by a strain of β hemolytic streptococci and a strain of enterococci when transferred in media with increasing concentrations of oleandomycin strains of staphylococci studied in a similar manner showed in one instance the slow progressive increase of resistance while two other strains emerged as highly resistant (greater than 4000 times the minimum inhibitory concentration) within the first three to seven transfers Sous et al[137] also demonstrated the development of significant resistance to oleandomycin after multiple transfers in media containing this agent

Additional reports[14 66 113 117] have shown clearly the ability of staphylococci to develop resistance to oleandomycin by in vitro procedures In contrast a study by Flanigan et al[49] did not show a significant increase in oleandomycin resistance of staphylococcal isolates before and after treatment with this agent these studies were performed by both the disc plate and the broth dilution methods

Sobin et al[13] pointed out initially that organisms resistant to penicillin streptomycin oxytetracycline chloramphenicol chlortetracycline polymyxin B or bacitracin were not resistant to oleandomycin however they reported one laboratory strain of staphylococci that demonstrated cross resistance to erythromycin and carbomycin Ross [119] in one of the earliest clinical reports

same phenomenon was observed in their studies with erythromycin Of the strains that were moderately resistant to oleandomycin there was a much greater difference between the two concentrations In the author s experience [49] the recovery of persistently viable cells occurred irregularly in tubes with concentrations of oleandomycin greater than the minimum bactericidal concentration studies were not performed to determine whether these were resistant mutants or chance survivors

Hobby and Lenert [9] studied the mode of action of oleandomycin on two strains of staphylococci and one *Streptococcus* they observed either a bactericidal or a bacteriostatic effect on multiplying bacterial cells The action of oleandomycin depended in part on the number of organisms present and/or the concentration of oleandomycin A more important factor in producing a bactericidal effect was the exposure of the bacterial cells for a minimum of five to seven hours before an appreciable decrease in the number of culturable cell units could be determined This suggested to them that the bactericidal action of oleandomycin is related to the gradual depletion of some essential metabolites within the bacterial cell whose formation is interrupted or inhibited by the action of oleandomycin Oleandomycin was found to have no major effect on nonmultiplying bacterial cells

Oleandomycin as well as erythromycin novobiocin and spiramycin was observed to decrease the oxygen uptake or respiration of oxygen by the bacterial cells in proportion to the concentration of the antimicrobial present in the nutrient medium by Sous et al [137] This effect was noted primarily in cultures during the proliferative phase of growth and was not seen under resting conditions or in the absence of cell multiplication

Conditions Affecting In Vitro Activity Andrieu and his co workers[3] showed that oleandomycin was more effective as a bacteriostatic agent in an alkaline medium elevation of the *p*H from 6 to 8 was responsible for a sixteenfold increase in the bacteriostatic action as reflected in the percentage of survivors in relation to the concentration of antibiotic The bactericidal activity did not appear to be modified to any great extent by *p*H changes

The protein binding effects and the subsequent reduction in antimicrobial activity were reported for oleandomycin by Fust et al [54] They noted that the addition of 10 per cent or more serum or urine was responsible for a significant reduction in the antimicrobial activity of oleandomycin solutions The addition of 20 per cent urine also reduced the antibacterial effects of solutions of erythromycin carbomycin and tetracycline to a similar degree against the *Staphylococcus* in vitro Andrieu and co-workers also noted a significant reduction in the susceptibility of *Micrococcus pyogenes* var *aureus* 209 P and *Bacillus subtilis* ATCC 6633 when the concentration of serum varied in the media between 5 and 20 per cent

Bacterial Resistance The appearance of resistant strains of staphylo-

Waisbren and Strelitzer[143] reported on a four year study in which the sensitivities and cross resistances of staphylococci were evaluated by broth dilution techniques All of 154 strains found to be resistant to erythromycin initially were found to be resistant to oleandomycin on the other hand 31 strains resistant to oleandomycin originally showed approximately 53 per cent susceptibility to erythromycin More recently Koch and Lepley[52] presented data on 451 recent staphylococcal isolates that were coagulase positive cross resistance between oleandomycin and erythromycin occurred with 100 per cent of the strains when the resistance was initially noted for oleandomycin and with 55 5 per cent of the strains that were initially resistant to erythro mycin

It is obvious from these reports which originated in different locations that a wide variety of cross resistance patterns exist In England Garrod[58] demonstrated that resistance which occurs in vitro uniformly developed to both erythromycin and oleandomycin such a resistance pattern was desig nated double resistance and was similar to that described by the authors previously cited Clinical isolates frequently did not show uniform resistance to the members of the macrolide group and when the resistance against erythromycin or oleandomycin was limited to one or the other Garrod re ferred to this state as dissociated resistance Garrod was unable by laboratory methods to produce a dissociated pattern of resistance in vitro Garrod also described the strains showing dissociated resistance as unstable mutants culturing these strains in an antibiotic-containing medium permitted the growth of cells that were found to develop the typical double resistance

Garrod felt that the clinical use of any of the macrolide antibiotics might produce resistance and on the basis of the evidence to that time it was uncer tain whether the clinical use of oleandomycin or spiramycin might produce bacterial resistance to erythromycin He was concerned however that the use of an inferior drug to which resistance developed might readily eliminate the subsequent usefulness of a better agent

In Vivo Activity The original description of in vivo therapeutic activity of oleandomycin was made by Sobin et al [13] Experimental infections were pro duced by injecting streptococci or staphylococci by the intraperitoneal route treatment with oleandomycin was accomplished by the subcutaneous route A dosage of 30 mg /Kg permitted survival of 85 to 90 per cent of animals infected with staphylococci while a similar dosage permitted the survival of 100 per cent of animals infected with *Str pyogenes* ATCC 8668 Noyes and co workers[101] performed mouse protection tests against six different strains of *M pyogenes* injected intraperitoneally There was a high percentage of survivors noted against five of the six strains of staphylococci when a daily dosage of 100 mg /Kg was used for two days The in vivo results correlated well with the in vitro susceptibility tests

on oleandomycin described 22 strains of *M pyogenes* var *aureus* that were resistant to erythromycin but relatively sensitive to oleandomycin Noyes et al[101] reported on 100 clinical strains of *M pyogenes* in which less than 5 per cent were resistant to oleandomycin these strains tended to be resistant also to penicillin and erythromycin but not to novobiocin Resistance could be developed slowly to oleandomycin and strains that showed this resistance to oleandomycin were found also to be resistant to erythromycin and penicillin

Needham and Geraci[100] found that 72 per cent of erythromycin resistant clinical isolates of *M pyogenes* were susceptible to oleandomycin strains that were found sensitive to erythromycin were also observed to be sensitive to oleandomycin These workers were also able to develop cross resistance in the laboratory and organisms that were made resistant to either erythromycin or oleandomycin showed complete cross resistance

Jones et al[77] also demonstrated the development of resistance and cross resistance in vitro to erythromycin carbomycin spiramycin oleandomycin and streptogramin Cross resistance to the antibiotics occurred in similar degree for all of the agents except streptogramin staphylococci acquired resistance to streptogramin less rapidly and the resistance to streptogramin was associated with a corresponding increase in cross resistance to the other antibiotics Garrod and Waterworth[59] found complete cross resistance between erythromycin and oleandomycin in 15 of 45 erythromycin resistant strains of staphylococci tested Fust et al[5] also called attention to the problem of cross resistance in their studies with staphylococcal isolates in Germany

In 1957 Rantz and co workers[113] reported on 41 clinical isolates of which eight were resistant to erythromycin only one of the eight strains was quite susceptible to oleandomycin while another was moderately susceptible In this group of erythromycin resistant organisms 75 per cent were resistant to oleandomycin Four strains were subsequently selected for the development of resistance in vitro they were exposed to concentrations of oleandomycin at 5 μg and erythromycin at 2 μg /ml cross resistance to the heterologous agent was shown for these organisms

Petersdorf and co workers[109] commented on a tendency for the clinical isolates of staphylococci that were resistant to erythromycin to be resistant to oleandomycin but the cross resistance that was noted occurred irregularly Such resistance was observed in spite of the fact that no oleandomycin had been used in Johns Hopkins Hospital where this study was conducted English[37] collected 101 clinical isolates from many sources which were all resistant to erythromycin 73 per cent were susceptible to oleandomycin at a concentration of 3 12 μg /ml Phage typing permitted identification of 11 different strains of which approximately 70 per cent again were noted to be resistant to erythromycin all were found to be susceptible to the action of oleandomycin

Waisbren and Strelitzer[143] reported on a four year study in which the sensitivities and cross resistances of staphylococci were evaluated by broth dilution techniques All of 154 strains found to be resistant to erythromycin initially were found to be resistant to oleandomycin on the other hand 31 strains resistant to oleandomycin originally showed approximately 53 per cent susceptibility to erythromycin More recently Koch and Lepley[8] presented data on 451 recent staphylococcal isolates that were coagulase positive cross resistance between oleandomycin and erythromycin occurred with 100 per cent of the strains when the resistance was initially noted for oleandomycin and with 55 5 per cent of the strains that were initially resistant to erythro mycin

It is obvious from these reports which originated in different locations that a wide variety of cross resistance patterns exist In England Garrod[58] demonstrated that resistance which occurs in vitro uniformly developed to both erythromycin and oleandomycin such a resistance pattern was desig nated double resistance and was similar to that described by the authors previously cited Clinical isolates frequently did not show uniform resistance to the members of the macrolide group and when the resistance against erythromycin or oleandomycin was limited to one or the other Garrod re ferred to this state as dissociated resistance Garrod was unable by laboratory methods to produce a dissociated pattern of resistance in vitro Garrod also described the strains showing dissociated resistance as unstable mutants culturing these strains in an antibiotic-containing medium permitted the growth of cells that were found to develop the typical double resistance

Garrod felt that the clinical use of any of the macrolide antibiotics might produce resistance and on the basis of the evidence to that time it was uncer tain whether the clinical use of oleandomycin or spiramycin might produce bacterial resistance to erythromycin He was concerned however that the use of an inferior drug to which resistance developed might readily eliminate the subsequent usefulness of a better agent

In Vivo Activity The original description of in vivo therapeutic activity of oleandomycin was made by Sobin et al [13] Experimental infections were pro duced by injecting streptococci or staphylococci by the intraperitoneal route treatment with oleandomycin was accomplished by the subcutaneous route A dosage of 30 mg /kg permitted survival of 85 to 90 per cent of animals infected with staphylococci while a similar dosage permitted the survival of 100 per cent of animals infected with *Str pyogenes* ATCC 8668 Noyes and co-workers[101] performed mouse protection tests against six different strains of *M pyogenes* injected intraperitoneally There was a high percentage of survivors noted against five of the six strains of staphylococci when a daily dosage of 100 mg /kg was used for two days The in vivo results correlated well with the in vitro susceptibility tests

Fust et al[55] described the chemotherapeutic activity of oleandomycin in mice with oral as well as subcutaneous administration experimental infections were produced with the pneumococcus *Streptococcus Staphylococcus* enterococcus tubercle bacillus and a species of *Salmonella* Their report did not describe the methods by which infections were produced nor the dosage schedule of oleandomycin but good effects were recorded in treating infections due to the *Streptococcus* and *Staphylococcus* while adequate responses were observed against the pneumococcus and *Salmonella* Relatively minimal activity was demonstrated against the enterococcus and the tubercle bacillus in experimental infections The enterococcal infections responded better to oleandomycin than to penicillin erythromycin or carbomycin The anti tuberculous activity was observed only with massive dosages of oleandomycin In the treatment of staphylococcal nephritis in the rat oleandomycin excelled all other antibiotics except penicillin to which it was considered equal in activity These workers also described a favorable response to high dosages of oleandomycin in the treatment of African relapsing fever in the mouse

Andrieu and co workers described a favorable therapeutic effect with oleandomycin against experimental infections caused by the pneumococcus *Streptococcus* and *Staphylococcus* They found little activity against infections produced by *Salmonella schottmulleri Klebsiella pneumoniae* and *Trypanosoma equiperdum* The activity of oleandomycin in vivo was compared with those of erythromycin novobiocin and spiramycin in mice infected with streptococci pneumococci staphylococci and *Ery rhusiopathiae* Oleandomycin was found to be more effective when given by the parenteral route than by mouth relatively small dosages were effective against staphylococci higher dosages were required for the streptococci and maximal dosages were required for effective action against the pneumococcus and *Erysipelothrix* In their experience the relationship of the effective inhibitory concentrations in susceptibility tests did not parallel the CD_{50} in the experimental infections This led them to comment that reactions in vivo are more important for the evaluation of an antibiotic drug than the in vitro analysis

COMBINED ACTIVITY WITH OTHER ANTIBIOTICS In 1956 a provocative publication by English et al[10] described enhanced activity of a physical mixture of tetracycline base (67 per cent) and oleandomycin base (33 per cent) In vitro studies were performed against laboratory strains of *M pyogenes* var *aureus Str pyogenes Diplococcus pneumoniae Corynebacterium diphtheriae L monocytogenes B subtilis* and *Vibrio comma* a significantly lower minimum inhibitory concentration for three species was noted for the combination of antibiotics in comparison with tetracycline alone or oleandomycin In addition 21 antibiotic resistant clinical isolates of *M pyogenes* var *aureus* were also tested for the minimum inhibitory concentrations a significantly lower concentration for 9 of the 21 strains was shown for the combination

as against either tetracycline or oleandomycin singly These authors also demonstrated by the minimum inhibitory concentration a retardation in the emergence of resistant variants of a strain of *M pyogenes* and of *Str pyogenes* In addition in vivo studies indicated a higher percentage of protection in mice by the combination of antibiotics against one strain of *Str pyogenes* and four strains of *M pyogenes*

In 1957 Garrod [3] examined the responses of 115 strains of staphylococci to a 2 1 mixture of tetracycline and oleandomycin of these strains 56 were susceptible to oleandomycin 45 were susceptible to tetracycline and 14 were abnormally resistant to one or the other of these two antibiotics Garrod did not find in a single instance that the minimum inhibitory concentration of the combination was significantly lower than that of either of the antibiotics when acting alone Garrod also exposed six strains of staphylococci so as to develop resistance to tetracycline oleandomycin and the combination of the two these organisms were then tested for their susceptibility to tetracycline oleandomycin and the combination It was Garrod s conclusion that oleandomycin failed to interfere with the development of resistance of these organisms to tetracycline tetracycline appeared to be responsible for the major portion of the activity of the combination Garrod further suggested that additional study of the problem of combined action of oleandomycin and tetracycline was necessary before the claim for enhanced or synergistic activity could be established

Almost simultaneously with the publication of this article in England Levitt and Hubble[90] described the effects of this combination on the minimum inhibitory concentration of 30 isolates of recent clinical origin None of these isolates was found to be more favorably affected by the combination of drugs in vitro than by either oleandomycin or tetracycline when used alone

A report by Bellelli and DeCarlo[17] of in vitro studies included seven strains of *M pyogenes* that did not show more than one tube dilution difference in minimum inhibitory concentration from the inhibitory concentration of either tetracycline or oleandomycin In vivo studies with white mice against experimental intraperitoneal infections with four strains of *M pyogenes* gave results as follows combined tetracycline and oleandomycin 10 mg /Kg 17 of 32 animals protected oleandomycin 3 3 mg /Kg 7 of 32 animals protected tetracycline 6 7 mg /Kg 2 of 32 animals protected These authors concluded that synergism had been demonstrated since the combination of antibiotics *gave results greater than the arithmetical additive effects*

Wiesmann[147] reviewed the evidence for the effectiveness of combinations of antibiotics and also tested 10 strains of staphylococci against inhibitory concentrations of tetracycline and oleandomycin singly as well as in combination his results and conclusions were directly opposed to those of English et al [40] His results also suggested that an in vitro delay in the emergence of resistance

could be ascribed to this combination only if both agents were initially quite active against the test strain of staphylococci

Several months later Jones and Finland[74] published a long review on the effectiveness of antibiotic combinations and described three different experimental approaches to define the activity of such combinations Thirty four strains of staphylococci were tested for the minimum inhibitory concentrations of tetracycline erythromycin oleandomycin spiramycin and 2 1 mixtures of tetracycline with each of the other three agents Jones and Finland could not find any superior activity for the mixtures as compared with the individual antibiotics An additional study was performed to test different ratios of the paired drugs When equal parts of tetracycline and the macrolide drugs were employed or when two parts of the macrolide with one part of tetracycline were employed the minimum inhibitory concentrations for the different strains *of staphylococci were found to be the same or to vary only by a factor of two* except in certain isolated strains Since the twofold broth dilution method *which was employed in determining the minimum inhibiting concentration* may be considered to have an inherent error of method expressed by a factor of two no significant difference could be attributed to the combinations

Two additional pharmacological studies were performed by Jones and Finland in which the antibacterial activity of the plasma was assayed after the ingestion of the four agents alone and the combination of tetracycline with the other three agents these studies will be discussed later in the section on pharmacology but it will suffice at this point to indicate that no combination appeared to be superior in producing antibacterial activity in the plasma than the more effective agent of the combination

By the end of 1957 Fairbrother and Southall[44] in England confirmed Garrod s observations on the lack of synergistic activity with the combination of oleandomycin and tetracycline The Fifth Annual Symposium on Antibiotics in October 1957 became the sounding board for seven different groups to report their experiences with in vitro studies of the oleandomycin tetracycline combination [8, 8, 51, 94, 105, 1 0, 145] *Cimmino et al reported on 332 staphylo-*coccal isolates against which the combination appeared to exert greater ac*tivity than could be explained on a simple additive basis this conclusion was* based on calculations of the expected minimum inhibitory concentration and the ratio of expected to observed concentrations Strains that demonstrated a marked resistance to tetracycline showed smaller ratios of expected to observed concentrations Elliott and Hall[35] presented data on the minimum inhibitory and minimum bactericidal concentrations for 30 strains of staphylococci no synergism was evident but occasional additive activity was seen and no antagonism was shown by the mixture of oleandomycin and tetracycline when compared to the single agents McFadden and Schelhart[94] presented in vitro data on *145 organisms of which 38 per cent showed greater*

susceptibility to the combination than to the individual components this suggested to these authors some synergistic activity Oswald and Welch[10] presented data on 202 separate isolates with 49 different phage patterns this study was thought to show synergistic effects for the combination of oleandomycin and tetracycline in 32 per cent of the isolates Foulke and Romansky[51] found only 2 of 103 isolates of staphylococci to show activity suggesting synergism Ross et al[1 0] could not find evidence to support the concept of synergism in studies by in vitro methods as well as by in vivo responses to the action of a tetracycline oleandomycin mixture Rivera et al[117] could find no evidence for antibiotic synergism by use of the wet-disc susceptibility test Most recently Furesz et al [3] compared combinations of five antibiotics tetracycline and oleandomycin showed increased activity over the single agents in reference to the minimum inhibitory concentrations of 65 strains of staphylococci A greater number of strains were inhibited by lower concentrations of the combined antibiotics This combination was not so effective as others however

It is rather apparent from a review of these reports that additive and perhaps synergistic effects for the combination can occasionally be shown but when more rigid parameters for synergistic activity are imposed on these studies the action of the mixture appears to be more additive then synergistic

The entire problem of combined antibiotic therapy was the subject of many editorial comments during the year of 1957 and it is regrettable that some of these editorials suffer from a lack of the dispassionate scientific evaluation that such comments and writings deserved[4 8 10 13 47 144]

In addition to the evaluation of antibacterial activity of the oleandomycin tetracycline combination the combination of a sulfonamide and oleandomycin was studied by Grunberg et al[6] By in vitro studies with a gradient plate technique a combination of sulfisoxazole and oleandomycin was observed to give greater antibacterial activity than that observed with the individual agents in vivo studies with streptococcal staphylococcal and pneumococcal infections suggested supplemental activity of this pair of antimicrobials when the dosage ratio of sulfisoxazole to oleandomycin was 5 1

Hobby and co workers[r9] demonstrated by in vitro and in vivo studies the antimicrobial activity of oleandopen they found this salt active against many gram positive microorganisms which were also shown to be susceptible to penicillin and oleandomycin when used alone In addition some strains of *M pyogenes* var *aureus* that were resistant to the action of penicillin were found to be inhibited by this salt It was suggested on the basis of these studies that some enhanced chemotherapeutic action resulted at times by the use of this chemical combination

Seller[1 5] reported on the combined use of penicillin and oleandomycin in a 30 bed general surgical ward the pretreatment susceptibility to oleandomy

cin of 90 per cent of staphylococcal isolates decreased to a level of 60 per cent There were fewer staphylococci isolated from the routine cultures of the nose and skin and coagulase negative strains resistant to oleandomycin were isolated more frequently during the period of general administration of these agents A different mechanism was thought to be operative in the emergence of resistance to oleandomycin than to penicillin

The combination of chloramphenicol and oleandomycin was studied by Reedy and co workers [11] Three of 10 strains of *M pyogenes* were found to be more susceptible to a combination of these two antibiotics so as to suggest a synergistic activity several additional strains were found to show the effects of summation of these two antimicrobial substances No evidence for antagonism was found against the staphylococci

A report on the effect of oleandomycin alone and in combination with neomycin on the intestinal microflora was published by Shidlovsky et al [1 9] oleandomycin alone was effective in reducing the gram positive population of the gastrointestinal tract The combination of oleandomycin with neomycin appeared to be no less effective in reducing the gram positive bacterial count but no data were presented to demonstrate that the combination was more effective than neomycin alone in reducing this group of intestinal organisms

ANTIMICROBIAL ACTIVITY OF TRIACETYLOLEANDOMYCIN The antimicrobial activity of triacetyloleandomycin was described by English and McBride [39] The in vitro activity of triacetyloleandomycin was found to be less than that of the oleandomycin base for all organisms that were susceptible to oleandomycin Seven antibiotic resistant clinical isolates of staphylococci were found to require two to four times as much triacetyloleandomycin for minimum inhibitory effects as was needed for oleandomycin base The activity in vivo was studied by mouse protection tests against experimental infections of staphylococci Comparisons were also made with erythromycin chloramphenicol penicillin V and novobiocin An ED_{50} ranging from 36 to 105 mg/kg compared favorably with dosages required for the other antimicrobial agents Celmer and Hochstein [6] have shown that triacetyloleandomycin is deacetylated in vivo and that antimicrobial activity is ultimately due to the activity of oleandomycin This phenomenon was the basis for a study by English and Fink[38] as to the indications for the use of triacetyloleandomycin in epidemic staphylococcal infections in this study the susceptibility of 64 recent clinical isolates of epidemic varieties was described in reference to oleandomycin base activity

PHARMACOLOGICAL PROPERTIES

Absorption and Excretion of Oleandomycin in Animals The original description[135] of oleandomycin by Sobin et al indicated that effective serum levels

of oleandomycin in the rabbit were achieved on a dosage of 200 mg /Kg the peak concentration was obtained one hour after administration of the dose and a moderately rapid decline in activity of the serum was noted in the next five to seven hours

These findings in laboratory animals were extended by Fust and co workers[54] who pointed out the relatively low toxicity of single large doses of oleandomycin in mice rats guinea pigs and dogs It was their impression that oleandomycin was less toxic than erythromycin Almost simultaneously Esselier and Keith[4] reported on pharmacological studies in man which were carried out in cooperation with Fust and Bohni Esselier and Keith also *reviewed pharmacological investigations in dogs monkeys* and rats which showed no significant toxicity Studies of the absorption and distribution of the drug indicated that a maximum concentration was obtained in the blood two to four hours after oral administration with an effective bacteriostatic con centration being maintained six hours after administration The excretion was noted to occur mainly by way of the kidneys and partly through the liver into the bile The concentrations of oleandomycin in the urine and the bile were stated to be several times that noted in the blood

Andrieu et al studied the absorption of oleandomycin when administered orally to rabbits in a dosage of 250 mg /Kg a peak concentration of 24 µg /ml was noted within one hour The serum concentrations declined rapidly during the course of the next three to six hours so that at seven hours the concentration was only 1 µg /ml These authors also noted the elimination of oleandomycin by way of the biliary and urinary tracts concentrations ranging from 2000 to 5000 µg /ml were noted for bile and urine

Diffusion Into Body Fluids and Tissues in Animals Kazenko et al[80] per formed analyses on blood serum and tissues for the concentration of oleando-mycin in *Rhesus* monkeys Four hours after a 300 mg oral dose serum concentrations ranging from 50 to 80 µg /ml were noted High tissue concen-trations were noted in the kidney (870 µg /Gm of tissue) pancreas (705 µg /Gm) spleen (695 µg /Gm) liver (675 µg /Gm) and lung (515 µg /Gm) no significant concentrations were noted in the brain Twenty four hours after an oral dose of oleandomycin, the thyroid kidney lung and spleen were noted still to have concentrations greater than 10 µg /Gm of tissue A comparative study of oleandomycin phosphate and the hydrochloride was carried out in two series of rats no significant differences in tissue concen trations were noted between these two agents The liver showed the highest tissue concentration for both drugs Similar results were obtained in the dog These authors also studied the urinary excretion and found an average of 20 per cent of an oral dose excreted by rats in eight hours studies on dogs and monkeys permitted the recovery of slightly higher percentages of doses of oleandomycin in a 24 hour period The biliary excretion was studied with the

TABLE V

Average Serum Concentrations (μg /ml) after Intravenous Oleandomycin Sampling Periods after Injection [10]

Dose mg	10 min	30 min	1 hr	2 hr	4 hr
250	7 5	2 8	1 6	1 3	0 6
500	17 2	6 4	3 7	2 1	1 2

rat as the experimental animal approximately 10 per cent of an oral dose was recovered in rat bile within four hours

The penetration of oleandomycin into the eye was studied in rabbits by Dumas et al [33] after intravenous injection of 50 mg /Kg of oleandomycin the concentration in the aqueous humor of the eye was approximately one half that of the serum concentration at one two and four hours after injection After the subconjunctival injection of oleandomycin high concentrations were found in the aqueous humor but there was intense local reaction characterized by edema and focal necrosis These authors also noted that a corneal bath applied in a concentration of 20 mg /ml for five minutes resulted in a concentration in the aqueous humor of 7 2 μg /ml of oleandomycin within one half hour after completion of the bath these concentrations rapidly declined so that at two hours the concentration was only 2 2 μg /ml

Absorption and Excretion in Man A preliminary report on the absorption and excretion of oleandomycin in man was presented by Baadj et al [10] Two small series of 5 hospitalized patients each were studied after oral dosages of 0 5 Gm every four hours and 1 Gm every 12 hours Those patients receiving 0 5 Gm every four hours demonstrated measurable serum concentrations in one hour with a maximum concentration eight hours after the fourth and final dose on the first day Those patients receiving two doses of 1 Gm at a 12 hour interval demonstrated a maximum concentration of oleandomycin in the serum eight hours after the initial dose Concentrations of oleandomycin in the urine ranged from 2 5 to 2000 μg /ml The authors did not indicate the period of urinary collections but reported that 3 per cent of the administered oleandomycin was recovered in the urine

Shortly after this preliminary report Bernstein and Piller[19] published an extensive study of experimental pharmacological trials in man In one series of 10 patients a dose of 250 mg of oleandomycin was administered orally every four hours An average peak serum concentration of 2 9 μg /ml was obtained at three hours after administration 4 of these 10 patients failed to develop serum concentrations of 2 μg /ml or greater after multiple doses A second series of 10 patients was given 0 5 Gm of oleandomycin in a single oral dose Five patients failed to achieve concentrations greater than 2 μg /ml of serum of which 3 were noted to have less than 1 μg /ml anacidity and de

layed absorption appeared to be related to these low serum concentrations in 2 of the patients A third series of 7 patients was given 0 5 Gm orally of oleandomycin every four hours cumulative effects were noted with serum concentrations ranging from a low of 2 0 µg /ml to a high of 16 5 µg /ml of serum The average concentration two hours after any of the multiple doses was 9 9 µg /ml of serum An occasional serum concentration after repeat doses was found to be lower than the initial concentration These variations may be attributed to individual differences in absorption of the antibiotic and are similar to those previously noted for other antibiotics when given orally

Bernstein and Piller[19] also studied the results of parenteral administration In one series of 18 patients who were given an intravenous dose of 250 mg in a period of two to four minutes serum concentrations ranged from a low of 2 3 to a high of 13 6 µg /ml of serum within 10 minutes after administra tion Another series of 8 patients received 500 mg intravenously in a similar period of time The average serum concentrations for these two groups are compared in table V

These authors attributed the early decline of the serum concentrations to the equilibration of the serum with the tissues Studies were also made of two small series of patients who were receiving continuous intravenous administra tion of either 2 Gm or 1 Gm of oleandomycin per day Only 2 of 6 patients receiving 1 Gm of oleandomycin by continuous intravenous infusion showed concentrations in excess of 2 µg /ml of serum other patients in this group generally had concentrations of 1 µg /ml or less Those receiving 2 Gm daily were found to have concentrations in excess of 2 µg /ml in three out of four patient trials

Bernstein and Piller also followed the urinary excretion in 7 patients who received a 500 mg intravenous dose of oleandomycin Approximately 85 mg or 17 per cent of the dose was recovered in the urine within six hours after the injection A single intravenous dose of 250 mg permitted the average recovery of 45 mg or approximately 18 per cent of the dose within four to six hours after injection

Oleandomycin concentrations in serums after parenteral injections were also studied by McKinney[95] and by Asay and Koch [15] McKinney observed a group of 10 adults who had received a single dose of 100 mg intramuscularly Serum concentrations ranged from 0 03 to 0 95 µg /ml in those persons having measurable concentrations When a small group of 5 adults was fol lowed after repeated intramuscular injections every eight hours for 24 hours no evidence of cumulative action could be obtained since the average serum concentrations remained in the general range of 0 7 µg /ml Asay and Koch administered oleandomycin in dosages of 12 5 to 25 mg /Kg intramuscularly or intravenously to children ranging from 4 months to 18 years of age Eighteen samples collected at random through the first six hours after the

injection of 12 5 mg /Kg intramuscularly were found to have concentrations at one hour ranging from 2 5 to 4 μg /ml and at six hours, from 0 3 to 20 μg /ml of serum A similar study with a dose of 25 mg /Kg intramuscularly did not result in any significant increase in serum concentrations When an intravenous dose of 25 mg /Kg was administered, the concentration after one hour was found to range between 10 and 40 μg /ml of serum this concentration declined rapidly so that at six hours the range was found to be 1 2 to 10 μg /ml

Distribution in Body Fluids and Tissues of Man To date no studies are known to the reviewer that report the tissue concentrations of oleandomycin comparable to those studied in animals Data are available concerning the distribution of oleandomycin into the bile and the cerebrospinal fluid

During November 1956, the first studies on distribution in the cerebrospinal fluid were published by Bernstein and Piller[19] and Esselier and Keith[42] Bernstein and Piller presented 6 patients without meningitis in whom the spinal fluid concentrations of oleandomycin ranged from a low of less than 0 2 μg to a high of 1 4 μg /ml after an oral dose of 0 5 Gm Only 3 patients were noted to have a measurable level by the method employed for assay In general these concentrations were found to be approximately 10 per cent or less of those in the serum of blood samples collected at the same time Esselier and Keith reported six determinations on cerebrospinal fluid of pediatric patients without meningitis one hour after parenteral injection the cerebrospinal fluid concentrations ranged from 2 5 to 5 0 μg /ml and were generally two to four tubes lower than the blood serum concentrations in a twofold broth dilution test At six hours the fluid was noted to contain 1 2 to 2 5 μg /ml of oleandomycin

Lyons et al[43] administered 30 mg /Kg of oleandomycin intravenously in a period of 30 to 45 minutes to 7 patients with neurosurgical disorders Effective concentrations were noted in the cerebrospinal fluid in two to six hours A slower infusion was found to give poorer results In 3 patients treated for meningitis the ratio of the spinal fluid to the serum concentrations was approximately one half or one quarter after equilibration had occurred

The concentration of oleandomycin in the bile of human beings was initially reported by Bernstein and Piller[19] who found a range of less than 4 to 300 μg /ml of bile within one half to one hour after a 250 mg intravenous injection Assay of the fluid in the gall bladder in 2 cases yielded concentrations of 160 to 404 μg /ml the values appeared to be approximately four times greater than those noted in bile from the ducts Esselier and Keith[4] reported on the biliary concentration of oleandomycin after a 500 mg oral dose within three hours the concentration in A bile was noted to be 186 μg./ml as contrasted with 228 μg /ml in B bile Four hours after administration the A bile contained 257 μg./ml and the B bile, 182 μg /ml

A larger study on the elimination of oleandomycin by pathological biliary tracts in human beings was recently published by Uberti[14] In a group of 30 patients three different dosage regimens were employed prior to the sampling of bile in the gall bladder After single oral doses the highest biliary concentrations were obtained three to six hours after administration the concentrations in the bile were greater than those in the blood in 70 per cent of cases The biliary concentrations of oleandomycin in the first six hours were variable and ranged from 0 to 340 µg /ml in the bile for 250 mg doses and from 0 to 980 µg /ml for 500 mg doses When the oral dosage of 500 mg was repeated on a six hour basis for a total of 4 0 Gm 7 of 10 patients again demonstrated oleandomycin in the bile ranging in concentration from 165 to 1000 µg /ml as contrasted with blood concentrations of 0 to 14 µg /ml

Another group of 8 patients were studied after choledochotomy bile from the common duct was assayed for antimicrobial activity after three separate dosage regimens and at various intervals after surgical relief In general the concentrations were maximal six hours after single doses and were inferior to those noted for the cystic bile Concentrations were noted to be higher in those patients who had not had previous bouts of jaundice or evidence of hepatic parenchymal damage The recoveries of oleandomycin were proportional to the flow of bile

Uberti also noted that when stenosis of the cystic duct had occurred the cystic bile was lacking in antibiotic activity Further observations of patients with vomiting demonstrated that the oleandomycin content of hepatic duct bile was greater than in the bile of the gall bladder

The distribution volume of oleandomycin was studied by Spitzy and Hitzenberger[138] after an intravenous dosage of 100 mg of oleandomycin in 5 patients An absolute distribution volume of 53 800 ±15 000 ml was calculated to be 0 86 and based on previous relationships this would indicate a high distribution throughout intracellular fluid volumes as well as extracellular fluid The half life of oleandomycin in the blood was calculated as 1 05 hours

Physical and Chemical Combinations of Oleandomycin The initial biological studies on the combination of tetracycline and oleandomycin[40] included pharmacological studies in rabbits dogs monkeys and man In rabbits and dogs the intramuscular injection of a 2 1 physical mixture of tetracycline and oleandomycin on the basis of 10 mg /Kg resulted in a total antibiotic activity in the serum of 2 87 µg /ml in one hour The total activity decreased moderately rapidly through the next four to six hours Differential assays employing an organism resistant to tetracycline alone and another resistant to oleandomycin alone indicated that oleandomycin was acting primarily in the first three hours thereafter the antimicrobial activity in the serum in man was largely ascribed to the tetracycline present in the mixture A 600 mg oral dose resulted in a peak antimicrobial activity equivalent to 3 64 µg /ml

injection of 12.5 mg./Kg. intramuscularly were found to have concentrations at one hour ranging from 2.5 to 4 µg./ml. and at six hours from 0.3 to 2.0 µg./ml. of serum. A similar study with a dose of 25 mg./Kg. intramuscularly did not result in any significant increase in serum concentrations. When an intravenous dose of 25 mg./Kg. was administered the concentration after one hour was found to range between 10 and 40 µg./ml. of serum; this concentration declined rapidly, so that at six hours the range was found to be 1.2 to 10 µg./ml.

Distribution in Body Fluids and Tissues of Man. To date no studies are known to the reviewer that report the tissue concentrations of oleandomycin comparable to those studied in animals. Data are available concerning the distribution of oleandomycin into the bile and the cerebrospinal fluid.

During November, 1956, the first studies on distribution in the cerebrospinal fluid were published by Bernstein and Piller[19] and Essellier and Keith.[42] Bernstein and Piller presented 6 patients without meningitis in whom the spinal fluid concentrations of oleandomycin ranged from a low of less than 0.2 µg. to a high of 1.4 µg./ml. after an oral dose of 0.5 Gm. Only 3 patients were noted to have a measurable level by the method employed for assay. In general, these concentrations were found to be approximately 10 per cent or less of those in the serum of blood samples collected at the same time. Essellier and Keith reported six determinations on cerebrospinal fluid of pediatric patients without meningitis one hour after parenteral injection; the cerebrospinal fluid concentrations ranged from 2.5 to 5.0 µg./ml. and were generally two to four tubes lower than the blood serum concentrations in a twofold broth dilution test. At six hours the fluid was noted to contain 1.2 to 2.5 µg./ml. of oleandomycin.

Lyons et al[93] administered 30 mg./Kg. of oleandomycin intravenously in a period of 30 to 45 minutes to 7 patients with neurosurgical disorders. Effective concentrations were noted in the cerebrospinal fluid in two to six hours. A slower infusion was found to give poorer results. In 3 patients treated for meningitis, the ratio of the spinal fluid to the serum concentrations was approximately one half or one quarter after equilibration had occurred.

The concentration of oleandomycin in the bile of human beings was initially reported by Bernstein and Piller,[19] who found a range of less than 4 to 300 µg./ml. of bile within one half to one hour after a 250 mg. intravenous injection. Assay of the fluid in the gall bladder in 2 cases yielded concentrations of 160 to 404 µg./ml.; the values appeared to be approximately four times greater than those noted in bile from the ducts. Essellier and Keith[4] reported on the biliary concentration of oleandomycin after a 500 mg. oral dose: within three hours the concentration in A bile was noted to be 186 µg./ml. as contrasted with 228 µg./ml. in B bile. Four hours after administration the A bile contained 257 µg./ml. and the B bile, 182 µg./ml.

through the stomach These observations were extended to man by the same group and reported by Payne et al [103] when oleandopen was administered orally antimicrobial activity in serum was noted for a period of eight hours after ingestion of the drug The antibacterial activity of the serum during the first four hours after administration of the drug was attributed primarily to the penicillin present in this salt while thereafter the activity appeared to be due to the oleandomycin The addition of potassium penicillin G to oleando pen increased the activity of both penicillin and oleandomycin for at least seven hours after a 600 mg oral dose Jones and Finland[7] tested the antibacterial activity of plasma after the oral administration of penicillin oleandomycin or a combination of these two drugs the oleandomycin penicillin salt plus penicillin G was also studied No increased antibacterial activity of the plasma was noted after administration of the mixture or the salt of the two drugs when contrasted with penicillin alone Oleandomycin alone was the least active agent used but was capable of more prolonged activity than that noted for penicillin alone

Triacetyloleandomycin Antibacterial activity was found in the serum of dogs and mice after the oral administration of triacetyloleandomycin by English and McBride [39] they noted that oleandomycin base was absorbed somewhat more rapidly than triacetyloleandomycin but that the latter was responsible for higher concentrations throughout the sampling period from three to seven hours after ingestion of the drug In mice triacetyloleandomycin consistently produced evidence of greater antibacterial activity in all periods than was noted for oleandomycin

The initial pharmacological trials in patients were reported by Shubin et al [130] in a crossover study of 30 patients serum activity during the first three hours after oral doses was double or better than that after ingestion of oleandomycin base The higher levels for triacetyloleandomycin persisted through six hours and this finding led to another study in which it was noted that patients showed measurable antibacterial activity in the serum for as long as 12 hours after a single 500 mg dose On a dosage schedule of 250 mg every eight hours there was some suggestion of cumulative activity in the serum after the first 24 hours Urinary recoveries in a 24 hour period indicated a 10 2 per cent recovery for oleandomycin base as compared to 23 5 per cent for triacetyloleandomycin in the same persons These studies suggested better absorption and greater availability to the tissues of triacetyloleandomycin

Reisch et al[116] compared the concentrations and antibacterial activity of serum obtained two hours after the fourth of multiple doses of 500 mg of triacetyloleandomycin and erythromycin They found the concentrations to be approximately equal at this period of time 15 of the 25 subjects had concentrations of triacetyloleandomycin equal to or greater than those obtained after erythromycin The antibacterial activity was tested in serial dilutions

at four hours assay of the tetracycline activity indicated again that the oleandomycin was primarily exerting its activity in the first four hours

An extensive study of the effect on serum antimicrobial activity of antibiotic combinations of tetracycline with erythromycin oleandomycin, and spiramycin as compared with each of the individual antibiotics was published by Jones and Finland[74] The antibacterial activity of serum obtained from normal men to whom these antibiotics were given either singly or in combination was assayed against a sensitive hemolytic *Streptococcus* a tetracycline-sensitive *Staphylococcus* and a tetracycline resistant strain of *Staph aureus* these studies did not indicate that the combination of oleandomycin with tetracycline produced any greater activity than the same total dosage of the more active drug When these serums were tested against a tetracycline resistant *Staphylococcus* the presence of tetracycline may have reduced the activity of oleandomycin Additional studies were made to test ratios other than a 1 1 combination of these agents When a dose of 500 mg of tetracycline was ingested alone or when an addition of 250 mg of oleandomycin was made to the tetracycline dosage the antibacterial activity of the serum from the volunteers showed no significant difference These authors opposed the use of such mixtures on the basis that the use of such combinations encourages inadequate treatment and provides a false sense of security for the physician prescribing them Such combinations were thought to reduce the therapeutic effectiveness that might be expected when proper dosages of properly chosen antibiotics were used alone It was felt that this mixture would not provide any effective control over staphylococcal strains resistant to erythromycin and that resistance to the macrolide drugs might occur as the result of inadequate dosages

Ross et al[10] also tested the antimicrobial activity of serum after the ingestion singly or in combination of tetracycline and oleandomycin With serum bioassay by a laboratory strain *Staph aureus* 209 P all preparations demonstrated peak antimicrobial activity at two hours Tetracycline alone and the combination of oleandomycin with tetracycline showed sustained activity through the fifth hour Oleandomycin showed a lower activity which was not sustained through the late hours A similar result was obtained when the serums were tested against a β hemolytic *Streptococcus* These authors therefore concluded that the principal activity of the combination of drugs was due primarily to the presence of tetracycline

Oleandopen was found by Hobby and co workers[69] to result in prolonged antibacterial activity of the serum from dogs This material could be administered orally or parenterally with similar results in antibacterial activity of the serum Somewhat higher initial activity was noted for the combination which was attributed to the fact that this salt is relatively stable only slightly soluble in water and thus more available for greater absorption after passing

urinary recoveries were noted after triacetyloleandomycin than after oleando mycin Adequate antibacterial activity wa also noted in the serum of patients after triacetyloleandomycin

Toxicity or Side Effects as Reported in the Literature TOXICITY STUDIES IN ANIMALS Initial reports of the toxicity of oleandomycin in laboratory animals were made by Fust and co workers [4] In comparative studies in the mouse rat guinea pig and dog the LD_0 for the various routes of administration indicated that oleandomycin was an agent of relatively low toxicity the values for the LD_0 in the different species and by the different routes of administra tion are shown in table VI When toxic dosages were administered intra venously the symptoms of ataxia increased excitability and irritability and ultimately tonic and clonic convulsions appeared On the basis of these studies and comp irison with similar studies with erythromycin these authors con cluded that oleandomycin was less toxic than erythromycin In a tolerance study young male rats were followed for a period of 13 weeks with a diet to which oleandomycin had been added to permit a daily dosage between 100 and 200 mg /Kg no serious intolerance was noted A slight but diffuse loss of hair was noted after the ninth week but no other toxic symptoms were observed Additional studies indicated that there was no appreciable toxicity for the blood bone marrow liver kidney adrenals testes lungs spleen heart thymus or pancreas Experimental toxicological studies after intra venous and oral administration of oleandomycin in laboratory animals were reported by Sorenson et al [136] Oleandomycin appeared to be well tolerated by the oral route when administered to rats dogs and monkeys for extended periods of time no specific organ toxicity was noted after this antibiotic Subcutaneous injections of 5 to 10 per cent solutions of the monohydrochlo ride salt twice daily for five days a week were found to be quite irritating to the tissues and therefore of no practical value Reduction of the concentration of the oleandomycin to 2 5 per cent and administration of dosages not in excess of 125 mg /Kg twice daily were better tolerated such injections were the maximal dosages that could be tolerated over a three week period without evidence of local tissue reaction

Acute toxicity studies for intravenous injections in rats indicated an LD_0 of 376 ±5 mg /Kg for the hydrochloride salt by comparison subcutaneous injections were found to have an $LD_{\ }$ of greater than 2000 mg /Kg The symptoms after toxic doses by the intravenous route in rats were immediate onset of muscular incoordination labored respirations and chronic convul sions with a relatively rapid recovery or death Similar acute toxicity studies in mice indicated a higher LD_{50} by the intravenous route No organ or tissue pathology was noted in rats dogs or monkeys that were found to be healthy at the start of the study 1 monkey which apparently demonstrated evidence of nephritis at the initiation of toxicity studies experienced a progression of

TABLE VI

LD₅₀ of Oleandomycin for Experimental Animals[84]
(expressed as mg/kg)

	Route	Dosage
Mice	Oral	8200
	Subcutaneous	2500
	Intravenous	600
Rats	Oral	10 000
	Subcutaneous	10 000
	Intravenous	440
Guinea pigs	Intraperitoneal	2343
Dogs	Intravenous	300

against *M pyogenes* strain 2891 14 subjects were found to have equal or greater antibacterial activity in the serum after triacetyloleandomycin as detected by the minimum inhibitory concentration Partial bacterial killing was noted by subculturing the serial dilutions of serum with some superiority for erythromycin in 16 subjects however the serum of 3 subjects failed to produce partial killing after erythromycin It was the impression of these authors that erythromycin and triacetyloleandomycin exhibited essentially the same pharmacological and antibacterial activity in the serum

A similar study by Kunin et al[84] compared the antibacterial activity of serum after oral triacetyloleandomycin erythromycin potassium penicillin V and penicillin V The results of this study indicated that triacetyloleandomycin and erythromycin gave fairly comparable antibacterial activity against a *Streptococcus* and a *Staphylococcus* that were used as test organisms These observations were true for serums of children as well as adults but activities of both of the macrolide drugs were found to be inferior to that resulting from the ingestion of penicillin preparations In general triacetyloleandomycin appeared to be absorbed somewhat faster as reflected by the greater antistreptococcal activity of serum samples in the first four hours when compared with erythromycin

In unpublished observations by Wright[151] serum concentrations of triacetyloleandomycin were found to be far superior to those of oleandomycin A similar comparative study by Mellman et al[97] indicated higher serum concentrations for triacetyloleandomycin as indicated by a cup plate assay the urinary recoveries after triacetyloleandomycin were double those noted after the administration of oleandomycin phosphate

As a result of all these comparative studies there can be little question that triacetyloleandomycin represented a distinct pharmacological advance over oleandomycin Superior serum concentrations and a higher percentage in

mg./Kg. The toxic symptoms in rats with intravenous dosage included depression, tremor, ataxia, pilomotor reaction, convulsions and respiratory depression. When triacetyloleandomycin was fed to rats in a diet, a depression of growth rate was observed only at the maximum concentration of 1 per cent which would be equivalent to a daily dosage of 250 to 500 mg./Kg. Fatty metamorphosis of the liver was noted in rats and monkeys on prolonged administration of diets with relatively high levels of triacetyloleandomycin. These changes were rapidly reversible and were noted to have returned to a normal state within one to two weeks after the triacetyloleandomycin was stopped. In dogs emesis could be provoked by administering daily dosages of 250 mg./Kg. body weight or more; dogs were apparently resistant to any change in the liver at this dosage level and did not show tissue damage or toxicity in any of the other organs studied.

TOXICITY STUDIES IN MAN. Oleandomycin, triacetyloleandomycin and the combination of oleandomycin with tetracycline have all been shown to have relatively low toxicity for man. The majority of problems encountered in the clinical administration of these agents are best classified as annoying side effects and are primarily related to the gastrointestinal system.

In reviewing the toxicity as described in papers by 14 different authors 1136 patient trials were noted with oleandomycin; side effects were encountered in approximately 3 per cent of these patients. Twenty-one patients were found to have side effects primarily related to the gastrointestinal tract which included nausea, vomiting, diarrhea, esophagitis and other mild gastrointestinal complaints. Esselier and Keith[17] described diuresis occurring in 12 patients with no renal or cardiovascular disease; these were primarily young adults and no explanation was given for the phenomenon observed. Two patients were observed to have a monilial overgrowth in the stool. Only 1 patient was found to have a skin reaction characterized by urticaria.

When oleandomycin was administered parenterally, at least 3 of 95 patients included in this group complained of definite irritation. Asay and Koch[15] had 2 patients in whom slight local irritation and erythema were noted at the site of intramuscular injection. Bernstein and Piller[19] also noted pain in 1 patient who received oleandomycin by the intravenous route; the pain was experienced along the course of the vein through which injection was accomplished. McKinney[9] did not state the exact number of patients who complained of pain after intramuscular injection but noted that many described immediate pain that persisted four to five hours at the site of injection.

Those authors who studied patients for toxicity of oleandomycin as reflected in the blood, liver function or renal function commented on the lack of specific toxicity for these organs. Only one skin reaction with urticaria suggested the possibility of allergic reaction.

At the present time there are relatively few papers in the literature that

this disease with emaciation multiple shallow ulcers and a chronic cystitis noted at the time of postmortem examination Sobin et al[13] also reported an LD_{50} of 550 mg /Kg for mice after intravenous administration of oleandomycin hydrochloride

The effect of oleandomycin on the oxygen consumption of tissues was studied by Carpi Tissue homogenates of the liver kidney and spleen of male rabbits previously given intravenous doses of oleandomycin were tested in the Warburg Barcroft apparatus in the presence and absence of glucose Oleandomycin was found to depress the oxygen consumption of these tissue homogenates maximal depression was noted after intravenous doses of 80 to 160 mg /Kg to the intact animal The presence of glucose in the system was accompanied by less depression of the consumption of oxygen by liver and kidney tissue but had little effect on the resulting depression on splenic tissue the depression of oxygen consumption after a 10 mg /Kg intravenous dose of oleandomycin was exaggerated in the presence of glucose These effects were similar but of lesser magnitude than those noted by Santarato for actinomycin C colchicine and desacetylmethylcolchicine but greater than those noted for sarcomycin

Sorenson et al[136] noted a depression of weight gain in rats to which oleandomycin was chronically fed in the diet Studies of weight changes in monkeys and dogs did not indicate any serious nutritional disturbance after prolonged oral administration of this drug Sherman et al[1 7] studied the effects of adding oleandomycin to poultry rations chicks were noted to have slightly greater weight gains when the diet was supplemented with oleandomycin than when no additive was present

The toxicity of the combination of oleandomycin phosphate and tetracycline was reported by Kaiser et al[78] on the basis of acute intravenous administration the LD_{50} for mice and rats was found to be 296 and 355 mg /Kg respectively Orally the LD_{50} was found to be greater than 5000 mg /Kg when this material was introduced by gastric gavage Chronic oral administration to dogs was not accompanied by any decline in weight and laboratory studies of blood cells fasting blood sugars nonprotein nitrogen and urine indicated no abnormalities Rats that were placed on a diet containing a combination of oleandomycin and tetracycline for a period of 16 weeks did not show any significant interference with growth rates except when the diet contained 2000 mg /Gm of the drug combination per 100 Gm of food In limited histopathological studies on 1 dog and 2 rats no evidence of growth or histological abnormalities was found attributable to the drug

The acute and chronic toxicity of triacetyloleandomycin was recently reported by Pan et al[10] The LD_{50} for intravenous administration of this material to mice and rats was 198 and 117 mg /Kg respectively the oral toxicity was low and no mortality was encountered with dosages as high as 500

tions Oleandomycin and tetracycline individually were responsible for reactions in only 1 or 2 more patients than the combination

From these reports it can be stated that oleandomycin triacetyloleandomycin and the combination of oleandomycin with the tetracyclines are relatively nontoxic agents and have a low rate of production of side effects Most of these side effects have been shown to be related to gastrointestinal dysfunction and to mild allergic skin disorders No serious hepatotoxicity or depressant effects on the hematopoietic organs or the kidneys have been noted Some irritation has resulted on parenteral administration of oleandomycin An ointment containing tetracycline and oleandomycin was found effective in topical applications with but little transitory irritation accompanying the application of this material

DOSAGE FORMS

Oleandomycin as the phosphate salt is available to the physician in capsular form for oral administration and in vials for solutions for injection by either the intravenous or intramuscular routes

The daily dosage of oleandomycin in adults has ranged from 1 to 3 Gm divided into four to six equal doses capsules of 250 mg permit this dosage with ease It has been shown that severe infections require intensive therapy and better results might be anticipated with a minimum of 2 0 Gm daily when an indication for therapy exists On such a regimen peak serum concentrations of oleandomycin from 2 0 to 16 0 μg /ml serum may be expected after repeated doses Urinary concentrations of oleandomycin may range from 2 5 to 1000 μg /ml over a 24 hour period [15]

The pediatric dosage initially used by Ross[119] was 40 mg /Kg /day in divided doses In a statement in New and Nonofficial Drugs which appeared in the *Journal of the American Medical Association* [9] a suggested dosage for children was 30 mg /Kg body weight The use of this preparation in pediatrics has largely been replaced by triacetyloleandomycin which is available in palatable suspension form

Oleandomycin phosphate for injection is a dry sterile powder which is to be dissolved in either sterile water physiological saline or isotonic glucose solution It may be given by the intravenous or intramuscular routes

Intravenous doses of 250 and 500 mg have been given safely [19] Such doses may be given at a rate of 20 mg /minute or as a slow infusion doses may be repeated every six hours or continued as an infusion for a 24 hour period [9] Maximum concentrations 10 minutes after completion of the injection of a single 500 mg dose have been observed between 12 and 21 μg /ml [19] Continuous infusions have resulted in serum concentrations of oleandomycin of 1 to 6 μg /ml The pediatric dosage of intravenous oleandomycin has been suggested at 40 mg /Kg /day [9] Asay and Koch[15] have found serum concentrations

describe the toxicity of triacetyloleandomycin Of 196 patients in three different series [3, 88, 130] who were treated by the oral route with this agent 11 patients were found to have gastrointestinal side effects characterized by nausea vomiting diarrhea and soft stools One case was reported by Isenberg and Karelitz[73] in which hepatitis occurred during the administration of oleandomycin the manifestations of this process subsided after discontinuation of the drug There have been no reports on parenteral administration

The combination of oleandomycin with tetracycline provided the reviewer with a much larger number of patients for the evaluation of toxicity A total of 1642 patients were included in 23 separate reports describing the oral use of this combination of agents Sixty one patients were found to have had side effects or mild toxicity attributable to the oleandomycin tetracycline combination by the oral route the rate of occurrence of side effects or toxicity was slightly less than 4 per cent As might be expected with the combination of two agents previously identified with gastrointestinal irritation the majority of patients (49 of 61 patients) had mild to moderately annoying symptoms referable to the intestinal tract 31 of these patients were noted to have had diarrhea Other symptoms referable to the gastrointestinal tract included nausea vomiting indigestion or dyspepsia distention flatus abdominal cramps glossitis and soft stools Eight patients were described as having either inflammation or pruritus referable to the vulvovaginal area 4 of these patients were found to have vaginal moniliasis Another 4 patients demonstrated the toxicity primarily in the skin as manifested by a skin rash in 3 and urticaria in 1

Manara and Gasparetto reported on preliminary trials with a water soluble combination of tetracycline and oleandomycin [94] When the drug was administered by intravenous intraperitoneal or intrapleural routes no toxic manifestations were observed for the liver blood cells blood sugar or renal activity They noted complete absence of allergic reactions and gastrointestinal disorders in 18 patients treated with this agent The only major problem arose with an irritant phlebitis after intravenous administration and was more commonly observed when 5 per cent glucose was used as a vehicle the phlebitis subsided promptly on conservative management and discontinuation of the therapy

The use of an ointment containing tetracycline and oleandomycin for topical therapy of skin infections was described by Kaneen and Cockcroft [9] Minimal transitory irritation was noted in some patients on application of this material no other toxicity was noted

Garfinkel and Gobianchi [7] tested the cutaneous reactivity of a group of allergic patients to 10 different antibiotics or combinations Penicillin produced the highest number and most severe reactions while the combination of oleandomycin and tetracycline had the lowest incidence and mildest reac

which include triple sulfonamides sulfisoxazole or a combination of analgesic agents Tablets containing 111 mg of each sulfapyrimidine and 75 mg of triacetyloleandomycin are available (Taomid*) an oral suspension is also available with the same antimicrobials in slightly different concentrations Tablets containing 333 mg of sulfisoxazole and 75 mg of oleandomycin are also available (Gantrimycin†)

USE IN STAPHYLOCOCCAL DISEASE

The initial clinical trials with oleandomycin were described by Ross[119] who found oleandomycin to be effective in the management of bacterial pneumonia and in staphylococcal enteritis Since that time a considerable number of papers have appeared in the literature describing the clinical effectiveness of this agent To facilitate the evaluation of oleandomycin as an antistaphylococcal agent an attempt will be made to review the application of this antibiotic to each of several broad classifications of staphylococcal disease

Skin and Soft Tissues The treatment of patients with staphylococcal infections of the skin and soft tissues with oleandomycin began almost immediately after its introduction Although oleandomycin was originally introduced in the United States the first extensive reports on the use of this antibiotic in the treatment of skin infections were made in Europe by Esselier and Keith[4] These authors reported on 412 patients who were treated in a period of 16 months with oleandomycin for a wide variety of clinical infections of these patients there were 10 with furunculosis 5 with abscesses and 2 with cellulitis All these patients showed a very satisfactory response to oleandomycin Eight of 10 cases of furunculosis were associated with staphylococcal isolates The abscesses that were treated with oleandomycin were found to contain staphylococci in 2 of the 5 patients and all were managed with surgical drainage in addition to the antibiotic therapy

Shortly thereafter Bunger and Schutze[9] reported a series of 90 patients treated with oleandomycin of which 9 patients were found to have furunculosis At least 3 of these were found to have staphylococci as the etiological organism 2 of the 3 patients were noted to have bacteriological isolates during the course of therapy which were proved by in vitro tests to have shown resistance to oleandomycin after initial susceptibility Siegenthaler et al[13] also reported on a group of skin infections treated with oleandomycin Thirty cases were found to have cultures of the lesions showing staphylococcal isolates and of these 21 patients demonstrated prompt response within two to three

---

* The trade name of J B Roerig & Co Division Chas Pfizer & Co for a combination of sulfapyrimidines and triacetyloleandomycin is Taomid

† The trade name of Hoffmann LaRoche for a combination of sulfisoxazole and oleandomycin is Gantrimycin

of oleandomycin ranging from 10 to 40 μg/ml after intravenous doses of 25 mg/Kg

Urinary recoveries after intravenous doses have been noted to be five to six times greater than those after oral administration

Intramuscular injections of 100 mg oleandomycin in saline result in peak serum concentrations of approximately 0 8 μg/ml in adults[93] In children *12 5 mg/Kg doses gave serum peaks between 2 5 to 40 μg/ml* increasing the dose to 25 mg/Kg resulted in slightly higher and better sustained serum concentrations[1]

Triacetyloleandomycin is available in capsules (125 and 250 mg), an oral suspension (125 mg/5 ml) and as pediatric drops (100 mg/ml), since it is rather insoluble no parenteral forms are available and oleandomycin phosphate is recommended when parenteral therapy is indicated

The recommended daily dosage for triacetyloleandomycin by mouth is the *same as that for oleandomycin phosphate*[9] *After single 500 mg. doses serum* concentrations have been noted to peak at about 2 0 μg/ml Repeat doses may be anticipated to give higher concentrations Reisch et al[116] observed antibacterial activity equivalent to 3 3 μg/ml of oleandomycin two hours after the fourth multiple dose of 500 mg every six hours Lower serum concentrations were obtained after 250 mg orally in repeated doses by Shubin et al[130]

The responses to administration of pediatric preparations indicate that an oral dosage of triacetyloleandomycin of 40 mg/Kg/day is quite adequate in staphylococcal infections[73] Doses of 10 mg/lb (22 mg/Kg) repeated every six hours were well tolerated by children and resulted in average peak serum concentrations of oleandomycin in excess of 2 4 μg/ml[97]

Combinations have been available with 1 part oleandomycin and 2 parts tetracycline in fixed proportions Oral preparations that formerly contained oleandomycin and tetracycline have been replaced by those substituting triacetyloleandomycin for the oleandomycin parenteral preparations retain the soluble oleandomycin phosphate These combinations are available as capsules for adults and as a sirup suspension and pediatric drops for children Glucosamine is also an additive in some preparations *

Dosages of these materials parallel those recommended for the single agents *Serum concentrations have been discussed previously in the section* on pharmacology differential assays of serum concentrations of the individual components add little to the general understanding of the clinical activity since in vitro tests of serum show that ingestion of the combination has little additive activity over that noted for tetracycline alone[74]

Additional combinations of triacetyloleandomycin are available for oral use

* The trade name of Chas Pfizer & Co for a combination of oleandomycin and tetracycline is Signemycin for the combination phosphate buffered Signemycin V for the combination with glucosamine Cosa Signemycin

other skin infections characterized by pyodermas or impetigos has been described by Kaneen and Cockcroft[79] and Cappelli[21] Cure or marked improvement in these skin conditions was noted in most instances in which the staphylococci were identified as the bacterial isolate Topical therapy with an ointment was employed by Kaneen and Cockcroft while conventional systemic therapy was utilized by Cappelli

There have been arguments advanced to implicate staphylococci in the perpetuation of severe acne It is not surprising therefore to find that antibiotics administered systemically have been tried in the control of this disease Shubin[1 9] described the use of the combination of oleandomycin and tetracycline for other conditions in 8 patients who had moderate acne vulgaris the acne cleared during this therapy and this was interpreted as being more impressive since these patients had only a fair response to prior therapy for the acne Stritzler and Frank[139] employed a low dosage regimen of the combination to treat acne 250 mg of oleandomycin tetracycline three or four times daily for three or four days up to one week was followed by 250 mg daily for periods ranging from one to six months Comparisons were made with tetracycline and oxytetracycline alone as well as with sulfonamides and another combination The most marked improvement after three months of therapy was noted with the tetracycline-oleandomycin combination or with tetracycline alone the fewest relapses occurred also after the use of the tetracycline oleandomycin combination These authors also noted that the smallest percentage of resistant organisms followed the use of tetracycline alone or the combination with oleandomycin They also concluded that antibiotics are just as effective in papular as in pustular acne

Other large scale trials of the combinations for acne were reported by Lewis et al[91] as well as by Cornbleet and Firestein [0] more than 80 cases of acne were treated in these two series with good results in approximately 80 per cent of the cases Details as to cultures and individual case responses are lacking in these reports

Hidradenitis suppurativa has been reported to be favorably influenced by oleandomycin and the combination of oleandomycin and tetracycline[134] A major problem in the evaluation of chemotherapy in this disease is apparently related to the lack of accurate diagnosis A total of 11 cases are included in reports[1 63 98 134] describing the use of the combination of oleandomycin and tetracycline with good results Cure of the chronic state or prevention of the development of multiple abscesses from the acute infection in the sweat glands has been reported by various observers with the combination

The use of oleandomycin in conjunction with tetracycline in the management of surgical infections of the skin was initially reported by LaCaille and Prigot[8] in a large series of cases in which either tetracycline or oxytetracycline was employed with oleandomycin less than 10 per cent of the patients

days of treatment and healing of the lesion within one week No new furuncles were noted during the course of therapy Five additional patients showed con siderable improvement while the remainder had less satisfactory responses or no response at all to this medication

More recently Muth and Weyer[93] reported a series of patients with derma tological infections including 27 cases of furunculosis The clinical response was quite satisfactory and similar to that described by other authors Shoch[1 4] also described a series of dermatological problems including 12 pyodermas Although no bacteriological identification of each of these cases was made 8 of the 12 patients healed promptly One was improved and 3 were not influenced by the administration of oleandomycin

The combination of oleandomycin with tetracycline has been reported in the United States more frequently than oleandomycin alone in the manage ment of staphylococcal skin infections Carter and Maley[3] utilized the com binations of oxytetracycline and oleandomycin or tetracycline and oleando mycin in the management of 74 patients from whom staphylococcal organisms were isolated a variety of soft tissue infections including cellulitis were listed but the report does not permit conclusions as to the effectiveness of these combinations in individual cases of staphylococcal skin disease Winton and Chesrow[1 0] described 24 cases in which staphylococci were isolated as pure cultures or as part of a mixed culture from a variety of soft tissue infections All of these patients responded satisfactorily and were controlled with thera peutic programs from 2 to 21 days in duration

The management of furunculosis with combined therapy was reported by Shubin[1 2] who treated 6 cases due to resistant staphylococci with 500 mg four times daily for one week and 250 mg four times daily for two weeks with excellent results Hagen and Scheffler[63] reported 5 cases of furunculosis due to hemolytic staphylococci which were handled with a regimen similar to that of Shubin Morador and Tate[93] employed dosages of 750 mg to 1 Gm /day of the combination in the management of 5 cases of furunculosis with cures obtained in all they noted a rapid subsidence of cellulitis and a halting of the necrotic pathology of this disease Many other authors[18 1 45 6 68 71 81 85 89 91 11] have includtd cases of furunculosis in their series of those treated with a combination of oleandomycin and tetracyclines in many of these cases the offending organism was not isolated and the role of staphy lococci can only be presumed There can be little doubt that the use of anti biotics in the more severe cases of furunculosis has met with some success but in the absence of a control series treated by the usual conservative hot soaks as well as by incision and drainage it is difficult to determine the effec tiveness of this combination Furthermore the superiority of the combination over the single antistaphylococcal drug has not been demonstrated

The use of oleandomycin and tetracycline combinations in the treatment of

adult as well as the pediatric group with excellent results in three to eight days Only 2 of these cases were positively identified with staphylococcal infection Four additional patients with furunculosis were treated by Isenberg and Karelitz [73] Three of the 4 showed satisfactory responses while 1 failed to respond to triacetyloleandomycin Mellman et al[97] reported 5 cases of pyo dermas and abscesses that responded to triacetyloleandomycin and from which staphylococci were isolated

The largest series of skin infections treated with triacetyloleandomycin was reported by Olansky and McCormick [103] a total of 61 patients with various skin infections showed approximately a 75 per cent response rate to this ther apy Best results were obtained in recurrent furunculosis and persistent recurrent pustular eruptions of the hands and feet Of 40 patients with pustular acne 25 were noted to have had excellent results and 9 had good results Although there was clearing of staphylococci and the acne bacillus during treatment with triacetyloleandomycin relapses were noted after cessation of therapy with reappearance of the organisms in the pustular lesions

Leming et al[88] reported a 100 patient trial of triacetyloleandomycin in a variety of skin infections from a surgical service Eighty three isolates of *Staph aureus* were obtained out of a total of 128 gram positive organisms from these lesions Only 1 patient was said to have had a fair response with excellent responses reported for 80 per cent of patients No failures were noted

It would appear that oleandomycin triacetyloleandomycin and the com bination of oleandomycin with one of the tetracyclines are all effective in the management of various staphylococcal infections of the skin In many of these conditions conservative management with heat hot soaks or surgical drain age is all that is required to control the infection but the prompt subsidence of inflammation and the prevention of extension of the lesion have been thought by many investigators to justify the use of these antibiotics Because of the short duration of therapy for these skin infections side effects or com plications have not been encountered frequently

Pneumonia and Empyema In the report of the initial clinical trials of olean domycin Ross[113] included 20 cases of bacterial pneumonia which responded satisfactorily None of these 20 cases was identified as being of staphylococcal origin Because of these successes in acute bacterial pneumonia it was natural to anticipate that oleandomycin would be effective in the treatment of staphy lococcal pneumonia

Bernstein and Piller[19] described 10 bacterial pneumonias and 1 case of empyema the latter and 1 case of bacterial pneumonia were found to be associated with staphylococcal isolates One patient had a bronchopneumonia superimposed on a picture of chronic emphysema of the lung and bronchitis he had already been treated for 13 days with penicillin during which time a

were shown to have bacterial isolates of pathogenic staphylococci All cases were apparently favorably influenced by the antibiotic combination but surgical intervention was not prevented however the magnitude and incidence of surgical intervention were thought to be reduced A comparison with series in which no antibiotic therapy was employed is not available

Morador and Tate[95] listed 20 patients with wound infections associated with *staphylococcal isolates 13 of these had pure cultures of staphylococci* while 7 patients were found to have mixed infections with a *Staphylococcus* as one of the isolates With a maximum daily dosage of 1 Gm of this combination cures were obtained in all of these patients Henne[69] also described the use of the combination of these drugs in the management of wound infections *with good results*

The topical application of a combination of oleandomycin and tetracycline in powder form to accelerate the rate of cicatrization of experimental wounds was reported by Signer and Vinci [133] *These results were similar* to those noted for erythromycin in a previous study

The treatment of abscesses with combinations of antibiotics including oleandomycin and one of the tetracyclines was reported by many authors [60, 6, 68, 81, 83, 89, 91, 111, 1, 1] Unfortunately it is not possible to determine from *these reports whether the combination of antibiotics is superior to either of* the agents alone Most reports also do not indicate whether surgical drainage was necessary in each instance It does appear likely however from the reports on the use of this combination of oleandomycin and tetracycline in the treatment of cellulitis that localized inflammatory tissue reactions may be *prevented from developing into abscesses*[85, 89, 1, 9] *and that extension of infection* can be controlled by the antibiotics

In the management of acute puerperal mastitis LaCaille and Prigot initially reported in 1956 the successful use of oleandomycin with either tetracycline or oxytetracycline in 7 patients More recently Febles and Biderman[16] described *good responses in 85 per cent of the patients treated with oleandomycin* and tetracycline Three of 20 patients showed relatively poor response with suppuration demanding surgical drainage an additional 3 patients required drainage although the response to the antibiotic must be considered good since suppuration had already developed prior to administration of the antibiotic These authors noted that *infection was limited* by the use of this antibiotic combination and that there were no complications resulting from the employment of this therapy

Triacetyloleandomycin has not received as many extensive clinical trials in the short interval since its clinical introduction however it has proved useful *in the management* of various skin infections [146] Shubin et al[130] treated 6 patients with furunculosis or cellulitis due to staphylococcal infection with rapid improvement in all instances *Wennersten*[146] *treated 15 patients in the*

gulase positive staphylococci Eight of these patients with staphylococcal piratory disease recovered completely with no sequelae One patient with coviscoidosis and superimposed staphylococcal bronchopneumonia showed provement while on the combination of oleandomycin and tetracycline this ent subsequently died after recovery from this acute respiratory disease o other infants (aged 6 and 7 months respectively) with mucoviscoidosis staphylococcal bronchopneumonia died while on treatment with this anti ic combination The relatively poor results obtained with most antibiotic mens in respiratory infections superimposed on mucoviscoidosis are not ouraging and the combination of oleandomycin and tetracycline has not erially improved the results with superimposed infections in this disease ara and Diaz[68] also reported on staphylococcal infections of the lower piratory tract but specific information is lacking on the pneumonic picture ountered and the clinical results

Acute bacterial pneumonias associated with staphylococcal infection have n successfully treated with triacetyloleandomycin[73 97 130 148] Isenberg and eltz[5] reported 10 cases of pneumonia due to *Staph aureus* with good lts on treatment with triacetyloleandomycin similar experiences were orted by Mellman et al[97]

would appear that excellent results can be obtained in the majority of s of acute bacterial pneumonias particularly those due to staphylococci n treatment is carried out with oleandomycin triacetyloleandomycin or combination of oleandomycin with tetracyclines The response obtained hese authors appeared to be somewhat slower than that generally obtained penicillin but there appeared to be no greater number of complications n these antibiotics were employed Severe underlying pulmonary pathol such as chronic bronchial disease or mucoviscoidosis reduced the effec ness of this antibacterial agent when a complicating pneumonia was ed this has been noted also for other antibiotics

small number of cases of empyema and pulmonary abscesses have been rted to have been successfully treated by oleandomycin[19 0 42 13] most ese cases had been associated with staphylococcal infections and required to three weeks of therapy for successful management of these illnesses orption of the effusion apparently occurred in some while surgical inter ion was necessary in other cases The duration of therapy for successful agement generally ranged between 14 and 25 days Bernstein and Piller[19] ted out the development of resistance to oleandomycin in 1 case of pul ary abscess that required prolonged therapy Since the emergence of tance has been shown to occur in vitro after several transfers of organisms nedia containing oleandomycin it would appear that there is sufficient nce to anticipate complications resulting from the emergence of resistance rganisms to this antibiotic The management of such cases warrants the

lung abscess developed The patient was then treated with oleandomycin 3 Gm daily for 7 days and 1 5 Gm daily thereafter Improvement was noted with diminution of fever a reduction in leukocyte count and a decrease in the amount of sputum On the eleventh day of therapy it was noted that the bacterial isolates demonstrated resistance to oleandomycin The patient with empyema had been treated for a month with penicillin and streptomycin owing to the development of resistance and the failure to respond completely the patient was then treated with oleandomycin Within 10 days the patient became afebrile A subsequent rise in temperature prompted rib resection and drainage of the empyema A second course of oleandomycin was undertaken after a 14 day interval in which no antibiotics were given the patient re sponded with the combined therapy but on the twenty third day after the second course of oleandomycin had been started new bacterial isolates were demonstrated to show marked resistance to this antibiotic

In the report of the extensive clinical trial of oleandomycin by Esselier and Keith [4] 15 patients with pneumonia and 7 patients with pleuropneumonia were found to have staphylococci as the major isolate in the sputum All these patients had a favorable response and apparently were no more difficult to treat than other bacterial pneumonias Within two to three days after the start of therapy significant clinical improvement occurred in the patients with pneumonia and marked roentgenological improvement was noted regularly in five to seven days The patients with pleuritic involvement required four to five days for the remission of fever and up to 14 days for major improve ment of lung shadows and pleural exudate Two cases of pleural involvement went on to form empyema but this resolved completely with oleandomycin Bunger and Schutze [9] also successfully treated 17 of 22 patients with bacterial pneumonia the bacteriological findings in these cases included pneumococci streptococci and staphylococci but the number of staphylococcal infections was not indicated in the paper Other reports of the use of oleandomycin in the treatment of pneumonias[89 110 11] are available but the bacteriological studies are not reported in sufficient detail to permit conclusions on the effec tiveness against staphylococcal pneumonia

Although a large number of authors[1 3 61 63 65 71 7 85 86 10 104 111 1 1 1 1 9 149] have reported on clinical trials with a combination of oleandomycin and the tetracyclines in patients with various diseases of the lower respiratory tract including acute bacterial pneumonia only an occasional case is described in sufficient detail to indicate a staphylococcal origin and an effective thera peutic result A notable exception is a report by Arneil[14] on the use of an antibiotic combination in the treatment of acute respiratory infection in child hood 8 children were severely ill with overwhelming infections while 42 children had acute respiratory infections of varying severity Eleven of 37 children from whom bacterial cultures were obtained were found to have

coagulase positive staphylococci Eight of these patients with staphylococcal respiratory disease recovered completely with no sequelae One patient with mucoviscoidosis and superimposed staphylococcal bronchopneumonia showed improvement while on the combination of oleandomycin and tetracycline this patient subsequently died after recovery from this acute respiratory disease Two other infants (aged 6 and 7 months respectively) with mucoviscoidosis and staphylococcal bronchopneumonia died while on treatment with this antibiotic combination The relatively poor results obtained with most antibiotic regimens in respiratory infections superimposed on mucoviscoidosis are not encouraging and the combination of oleandomycin and tetracycline has not materially improved the results with superimposed infections in this disease

Lara and Diaz[94] also reported on staphylococcal infections of the lower respiratory tract but specific information is lacking on the pneumonic picture encountered and the clinical results

Acute bacterial pneumonias associated with staphylococcal infection have been successfully treated with triacetyloleandomycin [73, 97, 130, 146] Isenberg and Karelitz[73] reported 10 cases of pneumonia due to *Staph aureus* with good results on treatment with triacetyloleandomycin similar experiences were reported by Mellman et al [97]

It would appear that excellent results can be obtained in the majority of cases of acute bacterial pneumonias particularly those due to staphylococci when treatment is carried out with oleandomycin triacetyloleandomycin or the combination of oleandomycin with tetracyclines The response obtained by these authors appeared to be somewhat slower than that generally obtained with penicillin but there appeared to be no greater number of complications when these antibiotics were employed Severe underlying pulmonary pathology such as chronic bronchial disease or mucoviscoidosis reduced the effectiveness of this antibacterial agent when a complicating pneumonia was treated this has been noted also for other antibiotics

A small number of cases of empyema and pulmonary abscesses have been reported to have been successfully treated by oleandomycin [19, 0 4, 13] most of these cases had been associated with staphylococcal infections and required two to three weeks of therapy for successful management of these illnesses Absorption of the effusion apparently occurred in some while surgical intervention was necessary in other cases The duration of therapy for successful management generally ranged between 14 and 25 days Bernstein and Piller[19] pointed out the development of resistance to oleandomycin in 1 case of pulmonary abscess that required prolonged therapy Since the emergence of resistance has been shown to occur in vitro after several transfers of organisms in media containing oleandomycin it would appear that there is sufficient evidence to anticipate complications resulting from the emergence of resistance of organisms to this antibiotic The management of such cases warrants the

use of maximal dosages (2 0 to 3 0 Gm /day) of oleandomycin to ensure early and prompt healing so as to avoid the problems of subsequent resistance

Several clinical reports[14, 6, 83, 1] are available that describe the use of a combination of oleandomycin and tetracycline in the management of empyema Santas et al[1] listed 2 cases of empyema of the chest associated with staphylococcal infections in which effective use of the antibiotic combination was made subsequent to decortication they also described 5 other cases of staphylococcal empyema that occurred postoperatively in a variety of surgical problems in which good results were obtained in 3 of the 5 patients The poor results were associated with intolerance of the drug in 1 instance and with a foreign body that interfered with the healing process in a second case These patients were treated for a period of 8 to 30 days and with dosages of the mixture ranging from 1 to 2 Gm /day Arneil[14] treated a 3 month old infant with staphylococcal tension pyopneumothorax by oleandomycin tetracycline combined therapy with good results An insufficient number of cases is reported in the literature to indicate that empyemas of staphylococcal origin are more successfully handled by a combination of oleandomycin and tetracycline than by oleandomycin alone A major advantage that might have been observed in these cases would have been the delay in emergence of resistance to oleandomycin

Approximately 10 patients with pulmonary abscesses have been treated with the combination of oleandomycin and tetracycline as reported by various authors [14, 63, 83, 1, 9] The bacteriology was not clearly associated with staphylococci in all of these cases but a relatively high response rate was noted in this small group of clinical trials Only 1 case to date has been reported in which a staphylococcal pulmonary abscess has been successfully treated with triacetyloleandomycin [130]

From these limited clinical trials it is suggested that oleandomycin and triacetyloleandomycin may be used successfully in the management of the more severe and complicated pulmonary infections in which empyemas and pulmonary abscesses are found Since resistance to the commonly employed antibiotics may readily occur in these diseases the oleandomycins may be substituted with anticipated effectiveness however since these diseases are associated with a slower response and a need for prolonged therapy the danger of the emergence of resistance of the infecting organism to oleandomycin cannot be overlooked The use of these agents should not be denied however on this theoretical basis The number of cases in which combination therapy of oleandomycin with a tetracycline has been employed is inadequate to make comparisons on the superiority of the mixture over the single drugs

Septicemia and Endocarditis Bacteremias, and especially those associated with endocarditis provide one of the most severe tests of clinical effectiveness for any antibiotic Because of the increasing frequency of antibiotic hyper

sensitivity reactions in patients and because there appears to be increasing resistance to many of the commonly employed antibiotics among clinical staphylococcal isolates—especially those in hospitals—it was fitting to employ oleandomycin in the treatment of bacteremias

Two of the 4 cases of sepsis reported by Esselher and Keith[4] were noted to have had positive blood cultures for *Staph aureus* in both instances previous antibiotic therapy had been ineffective One patient was treated for 42 days with 3 Gm of oleandomycin daily this patient became afebrile after three days and showed relatively rapid improvement with a diminution in leukocytosis and the absence of bacterial growth in subsequent blood cultures The second patient was treated for 20 days with 3 Gm of oleandomycin daily a clinical response was obtained within four days as the patient became afebrile These authors also noted the disappearance of associated urinary tract infection from which presumably the infection originally developed *Esselher and Keith[42] reported two other bacteremias and septicemias that were* not associated with staphylococcal infections but that responded to oleandomycin

Siegenthaler et al [13] in their description of 216 patients treated with oleandomycin had 4 cases of sepsis 3 of the 4 cases were associated bacteriologically with staphylococcal infection but only 2 were proved to have had positive blood cultures Of the 2 patients with positive blood cultures 1 had a satisfactory response to oleandomycin while the other showed a relapse after a temporary suppression of the bacteremia A patient with staphylococcal pyarthrosis was successfully treated although blood cultures were negative after the third day the continuation of fever and the local joint disease required surgical drainage The staphylococci recovered from the joint on the eighth day after initiation of oleandomycin therapy demonstrated significant resistance to this antibiotic at this time The second patient with staphylococcal bacteremia showed a response after three days with 3 Gm of intravenous oleandomycin daily thereafter 1 Gm intramuscularly daily for two days and 250 mg on the third day were administered prior to the change to oral therapy Within 36 hours there was a significant reduction in the number of staphylococcal colonies as detected on the blood culture plates however four days later there were as many colonies noted on culture as at the beginning of therapy It was noted also that the organism had emerged resistant to oleandomycin A critical review of this case led the authors to believe that inadequate therapy had been responsible for this treatment failure

Muth and Weyer[69] reported a case of staphylococcal sepsis in which an isolate resistant to penicillin and streptomycin was obtained from the sputum Prior to treatment positive cultures for staphylococci were obtained from cultures of the sputum stool urine and an abscess after therapy the sputum and urine remained sterile and the wound had healed

Bunger and Schutze [9] described a case of staphylococcal sepsis with associated diabetes mellitus This patient responded to oleandomycin only to have a second episode of bacteremia which responded to tetracycline therapy These authors also reported 1 case of staphylococcal endocarditis among 3 cases of endocarditis who recovered after being treated with oleandomycin a detailed description of the course of therapy was not given but a follow up six months later indicated the patient to be recovered from the disease

No other cases of staphylococcal endocarditis successfully treated with oleandomycin are known to the reviewer Esselier and Keith[4] as well as Porchet[110] have reported on oleandomycin in the successful treatment of endocarditis due to streptococci of either the α hemolytic or the nonhemolytic varieties

A few patients with bacteremia treated by a combination of oleandomycin and tetracycline have been included in several series of clinical trials [3 63 71 83] Four cases were noted to be associated with blood cultures of staphylococci 3 were apparently treated successfully One of these patients received a variety of antibiotic agents so that the exact role of the combination of oleandomycin and tetracycline in the therapeutic result cannot be completely defined No major differences in response to the combination of antibiotics as compared with oleandomycin alone could be determined in this small group

Two patients with endocarditis associated with staphylococcal isolates have been treated with combined antibiotic therapy One of these cases appears in the report of Cupples and Perry [31] their patient a 41 year old woman developed a septic state after a miscarriage Initially a cervical discharge was managed by antibiotic therapy and temporary improvement was noted she was discharged from the hospital on the twelfth day She was readmitted 7 days later with fever heart murmur slight anemia and a suggestion of splenomegaly A blood culture taken on admission subsequently demonstrated growth of a *Staph aureus* Treatment initially consisted of penicillin and novobiocin Failure to respond by the tenth day prompted the use of chloramphenicol which was later augmented by therapy with erythromycin After five weeks of unsuccessful antibiotic therapy the patient was placed on oleandomycin and tetracycline The temperature responded within two days and remained within the normal range thereafter The patient received 500 mg of the mixture of drugs every four hours for a total of 74 days a total dosage of 222 Gm of the mixture was used The patient had negative blood cultures during the course of therapy and for a four day period after the completion of therapy A three month follow up indicated that the patient had recovered from the infection although there was residual heart disease

Hoffman[71] listed 2 patients with endocarditis in his series of 73 patients treated with the combination of oleandomycin and tetracycline One of these patients was found to have a mixed culture of staphylococci and enterococci

therapy at a dosage of 2 Gm of the mixture per day did not influence the clinical course and the patient died after three days of ulcerative valvular endocarditis Another patient with endocarditis in their series was observed on blood culture to have a *Streptococcus viridans* and was successfully managed with the combination of the two drugs

To date the clinical experiences with triacetyloleandomycin as reported in the literature have not included any cases of bacteremia or endocarditis

In a panel discussion of the management of staphylococcal infections at the Sixth Annual Symposium on Antibiotics it was the consensus that oleandomycin appeared to be one of the weaker antistaphylococcal agents and therefore was not recommended nor found to be widely used in the management of severe blood stream infections and particularly those caused by staphylococci In summary the limited clinical trials with oleandomycin and with a combination of oleandomycin with tetracycline indicate the possible successful management of bacteremias when the infection appears to be due to staphylococci The few instances in which endocarditis has been treated with oleandomycin or the combination suggest that at best this drug is effective in only approximately 50 per cent of cases

Osteomyelitis The treatment of osteomyelitis with antibiotics has changed materially the management of patients with this disease the increasing incidence of resistant staphylococcal isolates has raised the problem of whether the gains in therapy of osteomyelitis can be maintained The use of each new effective antibiotic against staphylococcal infection has been pursued by the orthopedic surgeon

Essellier and Keith[4] first described the use of oleandomycin in osteomyelitis with the successful management of 3 cases out of 4 Three of the cases of osteomyelitis were associated with staphylococcal isolates 2 had been chronic cases of 8 and 12 years duration These patients were treated for 36 and 42 days respectively fever responded to therapy in eight days and a general improvement in drainage and closure of fistulas occurred Another case of osteomyelitis with a *Staph aureus* showed no significant response after 20 days treatment with oleandomycin in spite of the fact that the bacteriological isolates at this time showed a satisfactory sensitivity or susceptibility to oleandomycin

A greater number of authors[23 7 68 89 95 106 111 118 1 1 1 9 150 15] have commented on the use of oleandomycin in combination with tetracycline in the treatment of osteomyelitis A total of 79 cases of osteomyelitis were reported of which 39 could be positively identified as having *Staph aureus* in the drainage The results were described by the authors as excellent in 28 of these cases good in 22 fair or improved in 6 cases with treatment being continued and failure in 4 The responses of 19 of 25 patients in the series reported by Romana et al[118] were not described

Bunger and Schutze [9] described a case of staphylococcal sepsis with associated diabetes mellitus This patient responded to oleandomycin only to have a second episode of bacteremia which responded to tetracycline therapy These authors also reported 1 case of staphylococcal endocarditis among 3 cases of endocarditis who recovered after being treated with oleandomycin a detailed description of the course of therapy was not given but a follow up six months later indicated the patient to be recovered from the disease

No other cases of staphylococcal endocarditis successfully treated with oleandomycin are known to the reviewer Essellier and Keith[42] as well as Porchet[110] have reported on oleandomycin in the successful treatment of endocarditis due to streptococci of either the α hemolytic or the nonhemolytic varieties

A few patients with bacteremia treated by a combination of oleandomycin and tetracycline have been included in several series of clinical trials [3 63 71 83] Four cases were noted to be associated with blood cultures of staphylococci 3 were apparently treated successfully One of these patients received a variety of antibiotic agents so that the exact role of the combination of oleandomycin and tetracycline in the therapeutic result cannot be completely defined No major differences in response to the combination of antibiotics as compared with oleandomycin alone could be determined in this small group

Two patients with endocarditis associated with staphylococcal isolates have been treated with combined antibiotic therapy One of these cases appears in the report of Cupples and Perry [31] their patient a 41 year old woman developed a septic state after a miscarriage Initially a cervical discharge was managed by antibiotic therapy and temporary improvement was noted she was discharged from the hospital on the twelfth day She was readmitted 7 days later with fever heart murmur slight anemia and a suggestion of splenomegaly A blood culture taken on admission subsequently demonstrated growth of a *Staph aureus* Treatment initially consisted of penicillin and novobiocin Failure to respond by the tenth day prompted the use of chloramphenicol which was later augmented by therapy with erythromycin After five weeks of unsuccessful antibiotic therapy the patient was placed on oleandomycin and tetracycline The temperature responded within two days and remained within the normal range thereafter The patient received 500 mg of the mixture of drugs every four hours for a total of 74 days a total dosage of 222 Gm of the mixture was used The patient had negative blood cultures during the course of therapy and for a four day period after the completion of therapy A three month follow up indicated that the patient had recovered from the infection although there was residual heart disease

Hoffman[71] listed 2 patients with endocarditis in his series of 73 patients treated with the combination of oleandomycin and tetracycline One of these patients was found to have a mixed culture of staphylococci and enterococci

groups[9 126] in the treatment of urinary tract infections Approximately 140 patients were reported in these clinical trials Staphylococci were isolated from the urine of 19 patients with urinary infections Thirteen patients had good results with 4 of these apparent cures 5 patients were improved 1 case was complicated The dosage of oleandomycin in this mixture was limited to 0 45 Gm /day in one series a more vigorous regimen in the other series provided a daily dosage of 1 5 Gm of oleandomycin [1 6]

Of 16 patients treated with triacetyloleandomycin for urinary tract infec tions [97 1 0 146] only 2 were shown to have staphylococcal isolates the results were described as excellent for both patients [146]

From these results there can be little doubt that oleandomycin or triacetyl oleandomycin should be effective in urinary tract infections associated with susceptible staphylococci The dosage of combinations of oleandomycin with either tetracycline or sulfisoxazole may provide less than optimal tissue con centrations of oleandomycin if the staphylococci were resistant to the other member of the combination an unfavorable result with the combination might be explained The clinical results after large scale use of oleandomycin or the combinations will provide a better evaluation than is possible now however the chronicity of infection especially with stasis factors in the urinary system should make the physician wary of inadequate dosages of an antistaphylo coccal antibiotic

SUMMARY

Oleandomycin and triacetyloleandomycin have been shown to be clinically effective against a variety of infectious diseases associated with staphylococci Because of the low toxicity and infrequent side effects with these agents they should be considered in antistaphylococcal regimens The antibacterial activity of oleandomycin is somewhat lower than that of other agents but this should not be a deterrent to its use when staphylococcal isolates are found to be resistant to the commonly employed antibiotics The pharmacological superi ority of triacetyloleandomycin over oleandomycin makes it the choice for oral therapy whenever these drugs are indicated

Clinical indications for its use would certainly include infections of the skin respiratory tract and the urinary system when due to staphylococci or other susceptible gram positive bacteria The problem of cross resistance with other macrolide antibiotics should be sufficient reason for care in the use of oleandomycin or its derivatives for infections due to susceptible organisms the emergence of resistance of staphylococci to oleandomycin may also limit the use of other macrolide antibiotics Although it has been found to be effective in certain bacteremias and endocarditis it does not appear indicated except in rare instances the gravity of these infections should be reason for selecting the most potent antibiotic to which the organism is susceptible

The largest single series of patients with osteomyelitis was described by Ottolenghi et al,[100] the initial dosage employed by this group was 1 Gm of the mixture every 24 hours, the duration of therapy ranged from 14 to 78 days Four additional cases were reported in their series in which other gram positive organisms, chiefly streptococci were found as etiological agents None of the cases was characterized by gram negative bacterial isolates One cannot help but wonder whether equal dosages of oleandomycin alone would not have been equally effective or just as useful for therapy as was the mixture of oleandomycin and tetracycline

To the present time only 1 case of osteomyelitis has been reported as having been treated with triacetyloleandomycin [97] This was a 7 year old child who was successfully treated with triacetyloleandomycin when other antibiotic regimens had failed to bring about improvement The response in the first three weeks after initiation of triacetyloleandomycin was very gratifying and the child was ultimately discharged to continue therapy at home

From a survey of these results in the management of osteomyelitis it would appear that oleandomycin triacetyloleandomycin and the combination of oleandomycin with tetracycline are all effective in this disease Many of the acute cases of osteomyelitis showed dramatic clinical improvement so that surgical drainage was not necessary Chronic cases frequently showed marked clinical improvement so that additional operative procedures were entertained and performed with healing or marked improvement In spite of the chronicity of this disease the number of failures reported as the result of emergence of strains resistant to oleandomycin is relatively low for the total number of cases reported Unfortunately the lack of sufficient comparative studies does not permit a definitive conclusion on the merit of oleandomycin alone or com bined drugs with oleandomycin as the chief antistaphylococcal agent in the prevention of emergence of resistant staphylococcal isolates in the treatment of osteomyelitis

Urinary Tract Infections Staphylococci are occasional invaders of the uri nary tract Of 212 patients with urinary tract infections included in the reports of clinical trials with oleandomycin [19 0 4 110 13 141] 47 were found to have staphylococci in pure or mixed cultures Failure of treatment was noted in 6 cases while the remainder were improved or cured Sterilization of the urine was accepted as the criterion for cure

Ninety five patients with a wide variety of urinary tract infections were noted in seven reports[1 63 65 104 112 1 3 1 0] of clinical trials of the combina tion of oleandomycin and tetracycline Roughly one half of these cases were reported with identification of the etiological bacteria Only 17 patients were noted to have staphylococcal isolates The response was excellent in 5 patients satisfactory or controlled in 10 patients and fair in 2 cases

A combination of oleandomycin and sulfisoxazole was employed by two

groups[82 126] in the treatment of urinary tract infections Approximately 140 patients were reported in these clinical trials Staphylococci were isolated from the urine of 19 patients with urinary infections Thirteen patients had good results with 4 of these apparent cures 5 patients were improved 1 case was complicated The dosage of oleandomycin in this mixture was limited to 0 45 Gm /day in one series a more vigorous regimen in the other series provided a daily dosage of 1 5 Gm of oleandomycin [1 8]

Of 16 patients treated with triacetyloleandomycin for urinary tract infec tions [87 130 148] only 2 were shown to have staphylococcal isolates the results were described as excellent for both patients [146]

From these results there can be little doubt that oleandomycin or triacetyl oleandomycin should be effective in urinary tract infections associated with susceptible staphylococci The dosage of combinations of oleandomycin with either tetracycline or sulfisoxazole may provide less than optimal tissue con centrations of oleandomycin if the staphylococci were resistant to the other member of the combination an unfavorable result with the combination might be explained The clinical results after large scale use of oleandomycin or the combinations will provide a better evaluation than is possible now however the chronicity of infection especially with stasis factors in the urinary system should make the physician wary of inadequate dosages of an antistaphylococcal antibiotic

SUMMARY

Oleandomycin and triacetyloleandomycin have been shown to be clinically effective against a variety of infectious diseases associated with staphylococci Because of the low toxicity and infrequent side effects with these agents they should be considered in antistaphylococcal regimens The antibacterial activity of oleandomycin is somewhat lower than that of other agents but this should not be a deterrent to its use when staphylococcal isolates are found to be resistant to the commonly employed antibiotics The pharmacological superi ority of triacetyloleandomycin over oleandomycin makes it the choice for oral therapy whenever these drugs are indicated

Clinical indications for its use would certainly include infections of the skin respiratory tract and the urinary system when due to staphylococci or other susceptible gram positive bacteria The problem of cross resistance with other macrolide antibiotics should be sufficient reason for care in the use of oleandomycin or its derivatives for infections due to susceptible organisms the emergence of resistance of staphylococci to oleandomycin may also limit the use of other macrolide antibiotics Although it has been found to be effective in certain bacteremias and endocarditis it does not appear indicated except in rare instances the gravity of these infections should be reason for selecting the most potent antibiotic to which the organism is susceptible

The use of oleandomycin in fixed combinations with tetracycline and sul fisoxazole has been reported effective in all the previously mentioned clinical conditions associated with staphylococcal infections, staphylococcal meningitis has also been reported to have been successfully treated [50] Although inviting arguments can be presented for the use of fixed combinations it would seem that full therapeutic dosages are indicated whenever combined antibiotic therapy is justifiable The use of oleandomycin in combinations to delay the emergence of resistance in staphylococcal isolates is still lacking clinical justification

ACKNOWLEDGMENT

The author expresses his sincere appreciation for editorial comments and criticisms offered by Drs W D Celmer and E Steers Dr Celmer offered critical comments on the biochemistry of oleandomycin and its derivatives while Dr Steers offered over all criticism on the preclinical material

BIBLIOGRAPHY

1 Adams J Advantages of combined tetracycline-oleandomycin therapy in common infections J Tennessee M A *50* 446 1957
2 Andrieu G Monnier J Quercy J and Bourse R L Oleandomycin étude experimentale in vitro et premiers resultats cliniques Presse med *65* 865 1957
3 Anello V J and Gerschenfeld D S Septicopiohemia estafilococica en un nino tratamiento con la combinación oleandomicinatetraciclina Dia med *30* 51 1958
4 Anon Antibiotic combinations (editorial) Brit M J *2* 1418 1957
5 Anon Antibiotic combinations (editorial) Hawaii M J *16* 407 1957
6 Anon Antibiotic combinations (editorial) J M Soc New Jersey *55* 53 1958
7 Anon The antibiotic smog (editorial) Illinois M J *3* 324 1957
8 Anon Antibiotics galore (editorial) Brit M J *2* 150 1957
9 Anon Council on drugs Oleandomycin phosphate J A M A *168* 1011 1958
10 Anon The marriage of the moulds synergism in antibiotics oleandomycin and tetracycline (editorial) M Proc *3* 69 1957
11 Anon New combinations of antibiotics (editorial) Lancet *2* 1207 1957
12 Anon Oleandomycin tetracycline mixture (editorial) New England J Med *257* 289 1957
13 Antos R J Mycin schmycin (editorial) Arizona Med *14* 74 1957
14 Arneil G C Combination tetracycline-oleandomycin treatment of acute respira tory infection in childhood *In* Antibiotics Annual 1958-1959 New York Medical Encyclopedia Inc 1959 pp 327-332
15 Asay L D and Koch R An evaluation of parenteral oleandomycin in a pediatric hospital *In* Antibiotics Annual 1957–1958 New York Medical Encyclo pedia Inc 1958 pp 667–671
16 Baadj A G Corbin E E and Prigot A Observations on the absorption diffusion and excretion of oleandomycin in humans a preliminary report *In* Anti biotics Annual 1956–1957 New York Medical Encyclopedia Inc 1957 pp 72–74
17 Bellelli L and DeCarlo M On the antibiotic activity of PA 775 (association of PA 105 and tetracycline) Minerva med *48* 2705 1957
18 Bergdahl U Clinical experiences with the double spectrum antibiotic Sigmamy cin Svenska lak tidn *55* *1715* *1958*
19 Bernstein A and Piller M Über einige klinische und experimentelle Erfahr ungen mit Romicil (Oleandomycin) Schweiz med Wchnschr *86* 1247 1956
20 Bunger P and Schutze G Forschung und Praxis Klinische Erfahrungen mit Romicil (Oleandomycin) einem neuen Antibioticum Medizinische *51* 1811 1956

21 CAPPELLI E Clinical experience on the activity of a new antibiotic preparation Sigmamycin in dermatoses of infective origin (from pyogenes) Minerva med *48* 2690 1957
22 CARPI C Azione Della Oleandomicina Sul Consumo Di Ossigeno Di Alcuni Tessuti Animali Boll Soc ital biol sper *34* 297 1958
23 CARTER C H AND MALEY M C Application of tetracycline-oleandomycin and of oxytetracycline-oleandomycin in clinical practice *In* Antibiotics Annual 1956–1957 New York Medical Encyclopedia Inc 1957 pp 51-54
24 CELMER W D Triacetyloleandomycin biochemical correlations *In* Antibiotics Annual 1958-1959 New York Medical Encyclopedia Inc 1959 pp 277–283
25 CELMER W D ELS H AND MURAI K Oleandomycin derivatives Preparation and characterization *In* Antibiotics Annual 1957–1958 New York Medical Encyclopedia Inc 1958 pp 476–483
26 CELMER W D AND HOCHSTEIN F A Paper presented before the Division of Medicinal Chemistry 133rd meeting of the American Chemical Society San Francisco April 16 1958
27 CHIAPPARA P A case of sepsis with multiple osteomyelitis treated with a new antibiotic Minerva med *48* 2697 1957
28 CIMMINO A BONI A AND ORSI N Antibiotic activity of oleandomycin tetracycline combination in vitro study on 332 strains of *Micrococcus pyogenes* var *aureus* clinically isolated *In* Antibiotics Annual 1957–1958 New York Medical Encyclopedia Inc 1958 pp 708–715
29 COLVILLE J M COX F JR AND QUINN E L Comparative studies of oleandomycin triacetyloleandomycin and erythromycin with a brief review of the literature concerning oleandomycin *In* Antibiotics Annual 1958–1959 New York Medical Encyclopedia Inc 1959 pp 401–410
30 CORNBLEET T AND FIRESTEIN B Z Use of oleandomycin tetracycline (Signemycin) for acne AM&CT *4* 598–601 1957
31 CUPPLES J F B AND PERRY A W Acute staphylococcal endocarditis treated successfully with tetracycline-oleandomycin Canad M A J *77* 699 1957
32 DAVIS W G Report on tetracycline and oleandomycin used in combination Clin Rev *1* 21 1958
33 DUMAS J FIELDING I L AND ORMSBY H L Oleandomycin Am J Ophth *46* 10 1958
34 DURRIEU C A RODRIGUEZ J B AND PETRELLA E The use of tetracycline oleandomycin in buccal surgery *In* Antibiotics Annual 1958–1959 New York, Medical Encyclopedia Inc 1959 pp 297–299
35 ELLIOTT H J AND HALL W H Activity of oleandomycin salts mixtures and combinations against staphylococci *In* Antibiotics Annual 1957–1958 New York Medical Encyclopedia Inc 1958 pp 716–722
36 ELS H CELMER W D AND MURAI K Oleandomycin (PA 105) II Chemical characterization (I) J Am Chem Soc *80* 3777 1958
37 ENGLISH A R Oleandomycin cross resistance studies with clinical isolates of *Micrococcus pyogenes* var *aureus* *In* Antibiotics Annual 1957–1958 New York Medical Encyclopedia Inc 1958 pp 756–759
38 ENGLISH A R AND FINK F C Indications for the usefulness of triacetyloleandomycin in epidemic staphylococcal infections Antib & Chemo *8* 420–4?3 1958
39 ENGLISH A R AND MCBRIDE T J Triacetyloleandomycin biological studies Antib & Chemo *8* 424–428 1958
40 ENGLISH A R, MCBRIDE T J VAN HALSEMA G AND CARLOZZI M Biologic studies on PA 775 a combination of tetracycline and oleandomycin with synergistic activity Antib & Chemo *6* 511 522 1956
41 ESSELLIER A F AND KEITH J Le Romicil en médecine interne Méd et hyg *14* 520 1956
42 ESSELLIER A F AND KEITH J Romicil ein neues Antibioticum Schweiz med Wchnschr *86* 1311 1956
43 ESSELLIER A F AND KEITH J F Romicil ein neues Antibioticum (Oleandomycin phosphate) Schweiz. med Wchnschr *88* 314 1958
44 FAIRBROTHER, R. W AND SOUTHALL J E In vitro activity of Signamycin Lancet 2 974 1957
45 FARAH L Algunas Indicaciones Terapeuticas de la Sigmamycin Medicina *37* 519 1957

46 FEBLES D AND BIDERMAN I Antibiotic management of acute infections in the obstetric patient *In* Antibiotics Annual 1958–1959 New York Medical Encyclopedia Inc 1959 pp 270–272
47 FINLAND M The new antibiotic era for better or for worse? (editorial) AM & CT *4* 17–20 1957
48 FLANIGAN C JR LEMING B H., JR AND LAWRENCE J A study of possible in vivo oleandomycin resistance increase in *Staphylococcus aureus In* Antibiotics Annual 1958 1959 New York Medical Encyclopedia Inc 1959 pp 977 980
49 FOLTZ E L Unpublished observations on th antistaphylococcal action of erythromycin novobiocin and oleandomycin
50 FORADORI M On a case of Staphylococcus aureus meningitis superimposed on a tubercular meningitis treated favorably with Sigmamycin Minerva med *48* 2707 1957
51 FOULKE C W AND ROMANSKY M J An in vitro study of oleandomycin t tracycline mixture against 103 strains of hemolytic *Staphylococcus aureus In* Antibiotics Annual 1957–1958 New York Medical Encyclopedia Inc 1958 pp 732–737
52 FRANK, L AND STRITZLER C Newer antibiotics in the treatment of acne AM & CT *4* 419–421 1957
53 FURÉSZ S ZANGAGLIA O AND SCOTTI R The effect of fixed combinations of antibiotics on staphylococci in vitro Antib & Chemo *8* 571–575 1958
54 FUST V B BÖHNI E ZBINDEN G AND STUBER A Experimentelle Studien mit Oleandomycin und anderen Antibiotica Helv et med acta *23* 714 1956
55 FUST V B BOHNI E ZBINDEN G AND STUBER A Experimentelle Untersuchungen uber Oleandomycin Schweiz med Wchnschr *86* 1245 1956
56 GAGLIARDI B L antibiotic RO 2 7638 nell infezione difterica Minerva med *47* 1431 1956
57 GARFINKEL, M AND GOBIANCHI, A Prueba de sensibilidad a un grupo de agentes antibióticos en enfermos portadores de afecciones alergicas Jornada med *17* 115 1958
58 GARROD L P The erythromycin group of antibiotics Brit M J *2* 5036 1957
59 GARROD L P AND WATERWORTH P M Behaviour in vitro of some new antistaphylococcal antibiotics Brit M J *2* 61 1956
60 GEMMA G B MEL C AND BACHI V First experience with Sigmamycin in surgical infections Minerva med *48* 2643 1957
61 GILSANZ V PALACIOS J M SEGOVIA J M CRELS P S AND ELVIRO T Therapeutic value of combined tetracycline-oleandomycin Rev clin espan *67* 34 1957
62 GRUNBERG E DE LORENZO W F ELDRIDGE D AND TITSWORTH E Chemotherapeutic activity of combinations of sulfisoxazole and oleandomycin Proc Soc Exper Biol & Med *95* 144 1957
63 HAGEN H AND SCHEFFLER H Erste klinische Erfahrungen mit Oleandomycin und dem Doppelsp ktrumantibiotikum Sigmamycin Medizinische nr *14* 477 1957
64 HALL W H AND ELLIOTT H The effect of antibiotic combinations upon staphylococci with special reference to oleandomycin Proceedings Central Society Clini al Research 13th Annual Meeting Chicago Ill J Lab & Clin. Med *50* 822 1957
65 HAMMERL, V H Neue Wege in der Antibakteriellen Behandlung mit Antibiotikakombinationen Wien med Wchnschr *108* 629 1958
66 HASENCLEVER, H F Comparative in vitro studies of hospital strains of Staphylococcus aureus with oleandomycin tetracycline and an oleandomycin tetracycline mixture AM & CT *5* 14–18 1958
67 HAUKENES G AND TONDER O Oleandomycin Et Nytt Antibioticum Tidsskr f d norske laegefor *15* 627 1957
68 HENNE H F Klinische Erfahrungen mit dem Doppelspektrum Antibioticum Sigmamycin Med Klin nr *29* 1267 1958
69 HOBBY G L CELMER W D LENERT T F PIKULA VRABEC D DONIKIAN M A DALY J AND SARROCCO G The antimicrobial action of oleandopen the oleandomycin salt of penicillin G *In* Antibiotics Annual 1956–1957 New York, Medical Encyclopedia Inc 1957 pp 15–33
70 HOBBY G L AND LENERT T F Observations on the mode of action of oleandomycin *In* Antibiotics Annual 1957–1958 New York Medical Encyclopedia Inc 1958 pp 520–528

71 HOFFMAN H Klinische Erfahrungen mit dem Breitspektrum Antibiotikum Sigmamycin Medizinische *48* 1830 1958
72 HOZ FABRA J DE LA Preliminary results obtained in clinical experiments with Sigmamycin Rev clin espan *47* 101 1957
73 ISENBERG H AND KARELITZ, S Clinical and laboratory evaluation of triacetyloleandomycin in a variety of pyogenic infections *In* Antibiotics Annual 1958–1959 New York Medical Encyclopedia Inc 1959 pp 284–286
74 JONES W F JR AND FINLAND M Antibiotic combinations Tetracycline erythromycin oleandomycin and spiramycin and combinations of tetracycline with each of the other three agents—comparison of activity in vitro and antibacterial action of blood after oral administration New England J Med *257* 481 536 1957
75 JONES W F AND FINLAND M Antistreptococcal and antistaphylococcal activity of plasma of normal subjects after oral doses of penicillin oleandomycin and combinations of these antibiotics New England J Med *256* 115 1957
76 JONES W F JR AND FINLAND M Susceptibility of enterococci and of hemolytic streptococci of groups A B C and G to five new antibiotics in vitro Am J Clin Path *27* 5?8 1957
77 JONES W F JR NICHOLS R L AND FINLAND M Development of resistance and cross resistance in vitro to erythromycin carbomycin spiramycin oleandomycin and streptogramin Proc Soc Exper Biol & Med *93* 388 1956
78 KAISER J A MAZZARINO C BAJEK E M AND PAN S Y Oleandomycin tetracycline toxicity in experimental animals Antib & Chemo *7* 255–259 1957
79 KANEEN B AND COCKCROFT W H Clinical and bacteriological studies on Signemycin (oleandomycin tetracycline) ointment Canad M A J *78* 614 1958
80 KAZENKO A SORENSON O J JR WOLF L M DILL W A GALBRAITH M AND GLAZKO A J Physiologic disposition of oleandomycin in animals Antib & Chemo *7* 410–418 1957
81 KLOVSTAD O En Kombinasjon Av Oleandomycin Og Tetracyklin Tidsskr f d norske laegefor *77* 681 1957
8? KOCH M L AND LEPLEY D JR A report on incidence of coagulase positive hospital staphylococci exhibiting cross resistance between erythromycin and oleandomycin AM & CT *5* 549–552 1958
83 KRALJEVIC R PEARSON E AND BORGONO J M Investigation of the therapeutic value of the combination of tetracycline and oleandomycin AM&CT *5* 364–371 1958
84 KUNIN C M PRYLES C V AND FINLAND M Antibacterial activity of serum after oral doses of triacetyloleandomycin erythromycin potassium penicillin V and penicillin V Pediatrics *22* 422 1958
85 LACAILLE R A AND PRIGOT A Combinations of oleandomycin with oxytetracycline and tetracycline in the treatment of soft tissue infections a preliminary report *In* Antibiotics Annual 1956–1957 New York Medical Encyclopedia Inc 1957 pp 67–71
86 REBOLLEDO LARA M AND HEREDIA DIAZ J Further clinical studies with a combination of tetracycline and oleandomycin in the treatment of various infections *In* Antibiotics Annual 1958–1959 New York Medical Encyclopedia Inc 1959 pp 300–305
87 LEMING B H JR AND FLANIGAN C JR Correlation of sensitivity patterns of antimicrobial agents by the disc plate method a preliminary study involving 5600 gram positive cocci *In* Antibiotics Annual 1958–1959 New York Medical Encyclopedia Inc 1959 pp 414–417
88 LEMING B H JR FLANIGAN C JR AND ROY M K A clinical evaluation of triacetyloleandomycin in the treatment of infections due to gram positive cocci a preliminary report *In* Antibiotics Annual 1958–1959 New York, Medical Encyclopedia Inc 1959 pp 418–4?4
89 LEVI W M AND KREDEL F E A clinical trial of Sigmamycin in 50 cases of general surgical infections J South Carolina M A *53* 178 1957
90 LEVITT R O AND HUBBLE R H Antibiotic mixtures In vitro effect of a tetracycline-oleandomycin mixture (PA 775) on staphylococci New England J Med *257* 180 1957
91 LEWIS H H FRUMESS G M AND HENSCHEL E J Treatment of skin infections with tetracycline and oleandomycin Rocky Mountain M J *54* 806 1957

92 LIND H E AND TRAFTON H M Combined therapy in chronic urinary infec tions sulfisoxazole and oleandomycin *In* Antibiotics Annual 1957–1958 New York Medical Encyclopedia Inc 1958 pp 685-691
93 LYONS J J A MELAS M G AND COVERT S V Levels of oleandomycin and evaluation of clinical uses in abnormal cerebrospinal fluid systems *In* Antibiotics Annual 1957–1958 New York Medical Encyclopedia Inc 1958 pp 787–791
94 MCFADDEN H W JR AND SCHELHART D Comparison of the in vitro sensitivity of micrococci to oleandomycin tetracycline and a combination of oleandomycin and tetracycline *In* Antibiotics Annual 1957–1958 New York Medical Encyclopedia Inc 1958 pp 514-519
95 MCKINNEY B Unpublished observations on intramuscular oleandomycin A study of the serum levels obtained and side effects produced by this method of administra tion 1958
96 MANARA G AND GASPARETTO A The first clinical experience with water soluble Sigmamycin Minerva chir *13* 535 1958
97 MELLMAN W J BARNESS L A AND FOLTZ E L Triacetvloleandomycin in the therapy of pediatric infections *In* Antibiotics Annual 1958–1959 New York Medical Encyclopedia Inc 1959 pp 319-326
98 MORADOR J L AND TATE L S Treatment of fifty two cases of infections caused by coagulase positive staphylococci with a combination of oleandomycin and tetra cycline *In* Antibiotics Annual 1957–1958 New York Medical Encyclopedia Inc 1958 pp 702-707
99 MUTH H W AND WEYER H Clinical experiences with oleandomycin Ther Gegenwart *97* 142 1958
100 NEEDHAM G M AND GERACI J E Laboratory studies of oleandomycin (Matro mycin) AM&CT *3* 334-335 1956
101 NOYES H E NAGLE C S JR SANFORD J P AND ROBBINS M L Novobiocin and PA 105 in vitro and in vivo studies on effectiveness against *Micrococcus pyog enes* Antib & Chemo *6* 450–455 1956
102 O HERLIHY F C A clinical trial with Sigmamycin Med Press *140* 897 1958
103 OLANSKY S AND MCCORMICK G E JR Triacetyloleandomycin its use in the treatment of acne and pyodermas caused by resistant *Staphylococcus aureus In* Antibiotics Annual 1958–1959 New York Medical Encyclopedia Inc 1959 pp 265–267
104 OLMER J AND CASANOVA P Notes therapeutiques essais cliniques de la Sig mamycine àpropos de 59 malades traites Semaine d hop Paris *34* 1 1958
105 OSWALD E J AND WELCH H Antibiotic combinations III In vitro effects of oleandomycin tetracycline on two hundred and two cultures of *Micrococcus pyog enes* var *aureus In* Antibiotics Annual *1957–1958* New York Medical Encyclo pedia Inc 1958 pp 751–755
106 OTTOLENGHI C E FRIGERIO E R AND JIMENEZ, D S Tratemiento de la Osteomielitis Piogena por el PA 775 Bol y trab Soc de cir de Buenos Aires *26* 739 1957
107 PAN S Y DELAHUNT C S KAISER J A AND BAJEK, E M Triacetyloleando mycin acute and chronic toxicity in experimental animals Antib & Chemo *8* 528–534 1958
108 PAYNE H M HOBBY G L THORNHILL H TERRY N V HACKNEY R L SPURLOCK E SYPHAX G B DALY J SARROCCO G AND MACNEIL, M The antimicrobial activity of serum of human beings after the oral administration of the oleandomycin salt of penicillin G with and without added potassium penicillin G *In* Antibiotics Annual 1956–1957 New York Medical Encyclopedia Inc 1957 pp 34–43
109 PETERSDORF R G CURTIN J A AND BENNETT I L JR The sensitivity of two hundred strains of hemolytic Staphylococcus to a series of antibiotics A M A Arch Int Med *100* 927 1957
110 PORCHET A Erfahrungen mit Oleandomycin—Romicil Roche Praxis *46* 486 1957
111 RAGAZZINI F MOGGI P AND ACOCELLA M First clinical applications of Sigma mycin in pediatrics Minerva med *48* 2667 1957
112 RANDIG V K Einige Erfahrungen mit Sigmamycin Deutsches M J *8* 447 1957
113 RANTZ, L A RANDALL E THUM L AND BARKER L F The effects of vanco mycin oleandomycin and novobiocin and staphylococci in vitro Antib & Chemo *7* 399–409 1957

114 REEDY R J AND SHAFFER C H JR In vitro sensitivity of bacteria to novobiocin bryamycin oleandomycin vancomycin amphomycin bacitracin and synnematin B *In* Antibiotics Annual 1956–1957 New York Medical Encyclopedia Inc 1957 pp 483–485

115 REEDY R J WRIGHT W W OSWALD E J AND OSTROLENK M Antibiotic combinations in vitro effects on selected groups of bacteria II Combinations of chloramphenicol with sixteen other antibiotics *In* Antibiotics Annual 1957–1958 New York Medical Encyclopedia Inc 1958 pp 745–750

116 REISCH A J MARTIN W J NICHOLS D R AND HEILMAN F R Triacetylo leandomycin and erythromycin in serum comparison of concentrations and of antibacterial effects Proc Staff Meet Mayo Clin *33* 187 1958

117 RIVERA J A BRAME R E AND OSBORNE D Sensitivity of *Micrococcus pyog enes* from burned patients to oleandomycin and oleandomycin tetracycline com bined emergence of resistance to these antibiotics *In* Antibiotics Annual 1958–1959 New York Medical Encyclopedia Inc 1959 pp 411–413

118 ROMANA J DE ZALDIVAR C AND FALCONE F Actual therapeutic approach to the treatment of osteomyelitis *In* Antibiotics Annual 1958–1959 New York Medical Encyclopedia Inc 1959 pp 312–315

119 ROSS S PA 105 a new antibiotic some clinical observations *In* Antibiotics Annual 1955–1956 New York, Medical Encyclopedia Inc 1956 pp 600–603

120 ROSS S ZAREMBA E A AND PUIG J R Some comments on the lack of syner gism of tetracycline-oleandomycin mixture *In* Antibiotics Annual 1957–1958 New York Medical Encyclopedia Inc 1958 pp 723–731

121 SANGIUOLO F Therapeutic action of the tetracycline-oleandomycin (Sigmamycin) association Minerva med *48* 2679 1957

122 SANTAS A A GANORA H M AND BREA C M Tetracycline oleandomycin for prophylactic and therapeutic use in pleuropulmonary surgery preliminary report *In* Antibiotics Annual 1958–1959 New York Medical Encyclopedia Inc 1959 pp 306–311

123 SCHENONE H Genitourinary infections treated with the antibiotic combination tetracycline-oleandomycin *In* Antibiotics Annual 1958–1959 New York Medical Encyclopedia Inc 1959 pp 316–318

124 SCHOCH A Erste Erfahrungen mit dem neuen Antibioticum Romicil (Roche) in einer Dermatologisch Venerologischen Praxis Schweiz med Wchnschr *88* 742 1958

125 SELLER T F The effect of a new antibiotic upon a hospital staphylococcal people Clin Research *6* 150 1958

126 SEMANS J H AND GLENN J F Gantrimycin effective combined therapy of urinary infections J Urol *79* 1018 1958

127 SHERMAN W C DONOVAN G A REYNOLDS W M AND LUTHER H G Nutri tional evaluation of oleandomycin in poultry rations *In* Antibiotics Annual 1957–1958 New York Medical Encyclopedia Inc 1958 pp 256–258

128 SHIDLOVSKY B A MARMELL M AND PRIGOT A The effect of oleandomycin alone and in combination with neomycin on intestinal microflora *In* Antibiotics Annual 1956–1957 New York Medical Encyclopedia Inc 1957 pp 228–231

129 SHUBIN H Clinical evaluation of combined chemotherapy oleandomycin and tetracycline AM&CT *4* 174–178 1957

130 SHUBIN H DUMAS K AND SOKMENSUER A Clinical and laboratory studies on a new derivative of oleandomycin *In* Antibiotics Annual 1957–1958 New York, Medical Encyclopedia Inc 1958 pp 679–684

131 SIA C J AND BRAINARD S C Staphylococcus empyema in children Hawaii M J *17* 339 1958

132 SIEGENTHALER W KEISER G AND HEGGLIN R Klinische Erfahrungen mit Romicil (Oleandomycin) einem neuen Antibiotikum Deutsche med Wchnschr *81* 2074 1956

133 SIGNER A AND VINCI G G Sigmamicina e guarigione delle ferite Soc Med Chir Messina Year I *2 3* 1957

134 SNYDER, C C AND FARRELL, J J Hydradenitis suppurativa Plast & Reconstruct Surg *19* 502 1957

135 SOBIN B A ENGLISH A R AND CELMER W D PA 105 a new antibiotic *In* Antibiotics Annual 1954–1955 New York Medical Encyclopedia Inc 1955 pp 827–830

136 SORENSON O J JR FISKEN R A REUTNER T F WESTON K AND WESTON J K Experimental toxicological studies on oleandomycin Antib & Chemo 7 419–424 1957
137 SOUS H KRUPE W OSTERLOH G AND MUCKTER H Die Mittelspektrum Antibiotica Erythromycin Oleandomycin Novobiocin und Spiramycin unter experimentelle Bedingungen Arzneim forsch 7 386 1958
138 SPITZY K H AND HITZENBERGER G The distribution volume of some antibiotics In Antibiotics Annual 1957–1958 New York Medical Encyclopedia Inc 1958 pp 996–1003
139 STRITZLER C AND FRANK L Significance of the responses of acne vulgaris to antibiotics AM&CT 5 109–113 1958
140 TALBOT J R Experience with an antibiotic combination of tetracycline and oleandomycin used routinely for antiinfective therapy in an office practice Wisconsin M J 57 237 1958
141 TRAFTON H M AND LIND H E Oleandomycin in urinary tract infections AM&CT 4 703–707 1957
142 UBERTI E Sull eliminazione per le vie biliari patologiche dell uomo di un nuovo antibiotico (Romicil) Minerva chir 13 345 1958
143 WAISBREN B A AND STRELITZER C L A five year study of the antibiotic sensitivities and cross resistances of staphylococci in a general hospital In Antibiotics Annual 1957–1958 New York Medical Encyclopedia Inc 1958 pp 350–364
144 WELCH H A rational approach to combined antibiotic therapy (editorial) AM&CT 3 375–377 1956
145 WELCH H WRIGHT W W REEDY R J AND WINTERMERE D Antibiotic combinations in vitro effects on selected groups of bacteria I Combinations of oleandomycin with sixteen other antibiotics In Antibiotics Annual 1957–1958 New York Medical Encyclopedia Inc 1958 pp 738–744
146 WENNERSTEN J R Effectiveness of triacetyloleandomycin in a wide variety of infections AM&CT 5 527–532 1958
147 WIESMANN V E Antibiotica Kombinationen Schweiz med Wchnschr 32 1045 1957
148 WILLCOX R R Tetracycline and oleandomycin in combination in nongonococcal urethritis In Antibiotics Annual 1957–1958 New York Medical Encyclopedia Inc 1958 pp 672–674
149 WILLEMOT J P CUIGNIEZ J AND PANNIER R Sigmamycin in the treatment of pulmonary infections Bruxelles méd 38 1026 1958
150 WINTON S S AND CHESROW E J A clinical study of combined chemotherapy tetracycline and oleandomycin In Antibiotics Annual 1956–1957 New York Medical Encyclopedia Inc 1957 pp 55–62
151 WRIGHT W W Unpublished observations on a comparison of serum concentrations following erythromycin oleandomycin phosphate and triacetyloleandomycin 1958
152 ZALDIVAR CIRUJANO C G AND FALCONE ASISTENTE F Resultado preliminar de observaciones hechas en osteomielitis con la tetraciclina fosfato de oleandomycin (Sigmamycin) Rev Hosp niño 18 151 1957

136 SORENSON O J JR FISKEN R A REUTNER T F WESTON K AND WESTON J K Experimental toxicological studies on oleandomycin Antib & Chemo *7* 419–424 1957

137 SOUS H KRUPE W OSTERLOH G AND MUCKTER H Die Mittelspektrum Antibiotica Erythromycin Oleandomycin Novobiocin und Spiramycin unter experimentelle Bedingungen Arzneim forsch *7* 386 1958

138 SPITZY K H AND HITZENBERGER G The distribution volume of some antibiotics *In* Antibiotics Annual 1957–1958 New York Medical Encyclopedia Inc 1958 pp 996–1003

139 STRITZLER C AND FRANK L Significance of the responses of acne vulgaris to antibiotics AM&CT *5* 109–113 1958

140 TALBOT J R Experience with an antibiotic combination of tetracycline and oleandomycin used routinely for antiinfective therapy in an office practice Wisconsin M J *57* 237 1958

141 TRAFTON H M AND LIND H E Oleandomycin in urinary tract infections AM&CT *4* 703–707 1957

142 UBERTI E Sull eliminazione per le vie biliari patologiche dell uomo di un nuovo antibiotico (Romicil) Minerva chir *13* 345 1958

143 WAISBREN B A AND STRELITZER C L A five year study of the antibiotic sensitivities and cross resistances of staphylococci in a general hospital *In* Antibiotics Annual 1957–1958 New York Medical Encyclopedia, Inc 1958 pp 350–364

144 WELCH H A rational approach to combined antibiotic therapy (editorial) AM&CT *3* 375–377 1956

145 WELCH H WRIGHT W W REEDY R J AND WINTERMERE D Antibiotic combinations in vitro effects on selected groups of bacteria I Combinations of oleandomycin with sixteen other antibiotics *In* Antibiotics Annual 1957–1958 New York Medical Encyclopedia Inc 1958 pp 738–744

146 WENNERSTEN J R Effectiveness of triacetyloleandomycin in a wide variety of infections AM&CT *5* 527–532 1958

147 WIESMANN V E Antibiotica Kombinationen Schweiz med Wchnschr *32* 1045 1957

148 WILLCOX R R Tetracycline and oleandomycin in combination in nongonococcal urethritis *In* Antibiotics Annual 1957–1958 New York Medical Encyclopedia Inc 1958 pp 672–674

149 WILLEMOT J P CUIGNIEZ J AND PANNIER R Sigmamycin in the treatment of pulmonary infections Bruxelles méd *38* 10.6 1958

150 WINTON S S AND CHESROW E J A clinical study of combined chemotherapy tetracycline and oleandomycin *In* Antibiotics Annual 1956–1957 New York, Medical Encyclopedia Inc 1957 pp 55–62

151 WRIGHT W W Unpublished observations on a comparison of serum concentrations following erythromycin oleandomycin phosphate and triacetyloleandomycin 1958

152 ZALDIVAR CIRUJANO C G AND FALCONE ASISTENTE F Resultado preliminar de observaciones hechas en osteomielitis con la tetraciclina fosfato de oleandomycin (Sigmamycin) Rev Hosp nino *18* 151 1957

136 SORENSON O J JR FISKEN R A REUTNER T F WESTON K AND WESTON J K Experimental toxicological studies on oleandomycin Antib & Chemo 7 419–424 1957
137 SOUS H KRUPE W OSTERLOH G AND MUCKTER H Die Mittelspektrum Antibiotica Erythromycin Oleandomycin Novobiocin und Spiramycin unter experimentelle Bedingungen Arzneim forsch 7 386 1958
138 SPITZY K H AND HITZENBERGER G The distribution volume of some antibiotics In Antibiotics Annual 1957–1958 New York Medical Encyclopedia Inc 1958 pp 996–1003
139 STRITZLER C AND FRANK L Significance of the responses of acne vulgaris to antibiotics AM&CT 5 109–113 1958
140 TALBOT J R Experience with an antibiotic combination of tetracycline and oleandomycin used routinely for antiinfective therapy in an office practice Wisconsin M J 57 237 1958
141 TRAFTON H M AND LIND H E Oleandomycin in urinary tract infections AM&CT 4 703–707 1957
142 UBERTI E Sull eliminazione per le vie biliari patologiche dell uomo di un nuovo antibiotico (Romicil) Minerva chir 13 345 1958
143 WAISBREN B A AND STRELITZER C L A five year study of the antibiotic sensitivities and cross resistances of staphylococci in a general hospital In Antibiotics Annual 1957–1958 New York Medical Encyclopedia Inc 1958 pp 350–364
144 WELCH H A rational approach to combined antibiotic therapy (editorial) AM&CT 3 375–377 1956
145 WELCH H WRIGHT W W REEDY R J AND WINTERMERE D Antibiotic combinations in vitro effects on selected groups of bacteria I Combinations of oleandomycin with sixteen other antibiotics In Antibiotics Annual 1957–1958 New York Medical Encyclopedia Inc 1958 pp 738–744
146 WENNERSTEN J R Effectiveness of triacetyloleandomycin in a wide variety of infections AM&CT 5 527–532 1958
147 WIESMANN V E Antibiotica Kombinationen Schweiz med Wchnschr 32 1045 1957
148 WILLCOX R R Tetracycline and oleandomycin in combination in nongonococcal urethritis In Antibiotics Annual 1957–1958 New York Medical Encyclopedia Inc 1958 pp 672–674
149 WILLEMOT J P CUIGNIEZ J AND PANNIER R Sigmamycin in the treatment of pulmonary infections Bruxelles med 38 1026 1958
150 WINTON S S AND CHESROW E J A clinical study of combined chemotherapy tetracycline and oleandomycin In Antibiotics Annual 1956–1957 New York Medical Encyclopedia Inc 1957 pp 55–62
151 WRIGHT W W Unpublished observations on a comparison of serum concentrations following erythromycin oleandomycin phosphate and triacetyloleandomycin 1958
152 ZALDIVAR CIRUJANO C G AND FALCONE ASISTENTE F Resultado preliminar de observaciones hechas en osteomielitis con la tetraciclina fosfato de oleandomycin (Sigmamycin) Rev Hosp nino 18 151 1957

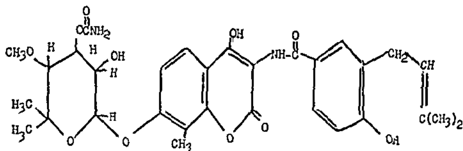


Fig 1 Structural formula of novobiocin

and Vulcamicina by Lepetit S p A of Milan, Italy the organism used by the workers of the latter firm was isolated from soil obtained in the vicinity of Rome [75]

The literature on novobiocin that was available to the author prior to the middle of 1957 has previously been reviewed and summarized elsewhere [81] The reader is referred to that monograph for most of the details and the bibliography only certain of these will be referred to here specifically

PHYSICAL AND CHEMICAL PROPERTIES

As the pure crystalline salt novobiocin has a slightly yellow to white color and a well defined and distinctive crystalline form It is soluble in aqueous solutions with *p*H greater than 7 5 and insoluble in more acid solutions In the acid form it is soluble in acetone ethyl or amyl acetate, ethanol or pyridine The dried material is slightly sensitive to light at room temperature Novobiocin has a unique chemical structure which consists essentially of a nine carbon sugar attached glycosidally to dihydroxymethyl coumarin The empirical formula of novobiocin is $C_{31}H_{36}N_2O_{11}$ and its structural formula is as shown in figure 1 [45, 47, 80]

Novobiocin is a dibasic acid and therefore neutral and acid metal salts can be prepared these retain their antibacterial activity although they vary some what in their physical characteristics [15, 46] The preparation generally employed for oral usage in capsules has been the monobasic sodium salt whereas the calcium salt which is somewhat more stable has been used to prepare sus pensions in flavored sirup for pediatric use

METHODS OF ASSAY

Methods used for the microbiological assay of novobiocin are similar in many respects to those used for most other antibiotics varying only in details The assay organisms generally used include *Bacillus subtilis* some standard strains of *Micrococcus aureus* *Sarcina lutea* and *Micrococcus pyogenes* var

albus the latter has been used by the Food and Drug Administration for pharmaceutical dosage forms [7] Both agar cup plate and turbidimetric methods in fluid media have been used and a colorimetric method is also available [7] The serial dilution method is the one most often used with serums and body fluids

ANTIBACTERIAL ACTIVITY IN VITRO

In general the antimicrobial spectrum of novobiocin[31] closely resembles that of penicillin and of erythromycin although its action is not related to either of them novobiocin is active against many strains that are naturally resistant to these agents and against strains made resistant to them by exposures in vitro The major activity of novobiocin is against pathogenic strains of *Staphylococcus aureus* such strains are generally more sensitive to this antibiotic than to any other except penicillin and novobiocin is as active against penicillin resistant and erythromycin resistant strains as it is against strains that are sensitive to these antibiotics The same is true of staphylococci both sensitive and resistant to streptomycin the tetracyclines and chloramphenicol Among pathogenic staphylococci isolated from a variety of clinical sources in which previous exposure to novobiocin can be excluded *nearly 90 per cent are inhibited by this antibiotic in concentrations of 1 0* μg or less per ml and these include strains that are moderately or highly resistant to one or more of the other widely used antibiotics Most of the remaining strains of *Staph aureus* that have been tested are inhibited by 5 μg /ml or less although occasional strains (about 0 5 per cent) are not inhibited by 25 μg /ml

Pneumococci are about as sensitive to novobiocin as are staphylococci most strains are inhibited by 1 μg /ml or less but occasional strains have required up to 25 μg /ml Most hemolytic streptococci of group A are moderately or highly susceptible being inhibited by 5 μg /ml or less but some are not inhibited by 50 μg /ml Hemolytic streptococci of other groups and strains of *Str viridans* are slightly less susceptible most of them being inhibited by 1 to 10 μg /ml Enterococci (group D streptococci) are the least susceptible of the streptococci some are not inhibited by 50 μg /ml but about one half of the strains are inhibited by 12 5 μg /ml or less *Corynebacterium* species including *Corynebacterium diphtheriae* are also quite sensitive most strains being inhibited by 5 μg /ml

Among gram negative bacteria the most susceptible to novobiocin are *Hemophilus influenza Hemophilus pertussis* and *Neisseria meningitidis* most strains of which are inhibited by 10 μg /ml or less Some strains of *Pasteurella* are susceptible to 12 5 μg /ml but those of *Brucella* have required 30 to 50 μg /ml Among the *Enterobacteriaceae* many strains of *Proteus* are inhibited by 25 μg or less but most other strains of *Proteus* most strains of

Escherichia coli Aerobacter aerogenes Klebsiella pneumoniae various species of *Salmonella Shigella* and *Pseudomonas* require higher concentrations or are resistant to 100 or even 400 μg /ml

Mycobacteria are only slightly sensitive some strains of *Mycobacterium tuberculosis* however are inhibited by 10 μg /ml or even less, but others are resistant to 30 to 60 μg /ml and this is true of most atypical strains of mycobacteria [100]

Most of the tests for sensitivity to novobiocin have been carried out in appropriate liquid media that support good growth of the organisms but tests can also be done on solid media into which varying concentrations of the antibiotic are incorporated or by the use of impregnated paper discs the latter are convenient for screening purposes and have been applied in clinical bacteriological laboratories Using such discs 8 mm in diameter, onto each of which was placed a standard drop (0 02 ml) of a solution containing 10 μg /ml Fairbrother and Williams [8] tested 1100 strains of various species These included 470 strains of *Staph aureus* 17 of group A hemolytic streptococci 19 of *Diplococcus pneumoniae* and 12 of *H influenzae* all of these were found to be sensitive Only 50 per cent of 56 strains of *Streptococcus faecalis* a similar proportion of eight strains of *Neisseria gonorrhoeae* and one of two strains of *Hemophilus parainfluenzae* were sensitive by this method i e produced a zone of inhibition around these discs All of 310 strains of various coliforms 144 of *Proteus* 40 of *Pseudomonas pyocyanea* 8 of *Shigella sonnei* and 14 of various fungi were found to be resistant by the same method When added to potato dextrose agar in a concentration of 10 parts/million novobiocin suppresses soil bacteria and this has been used to isolate fungi from soil [44] On the other hand Sanford et al[76] tested 18 strains of *Nocardia asteroides* and found them to be inhibited by novobiocin in concentrations ranging from less than 0 8 to 10 μg /ml however they could not demonstrate any effect of the antibiotic against infections of mice with these organisms

A number of factors may influence the susceptibility of organisms to novobiocin in vitro Although most media that support equivalent growth give similar results in the tests for sensitivity differences have been noted in some media which may be related to certain divalent cations notably magnesium (as magnesium sulfate) that reverse the inhibition of gram negative bacteria by novobiocin this is not the case with gram positive bacteria [10] Increasing acidity of the medium within limits that still support good growth in control cultures results in progressively increased activity of novobiocin against *Staphylococcus Proteus* and *E coli* [55] This suggests that the effectiveness of therapy for urinary tract infections may be enhanced by procedures that result in acidification of the urine which is in contrast to the observations on treatment with streptomycin which indicate increased effectiveness with alkalinization of the urine

In liquid media the size of the inoculum of the test organism is important [8 34 5 6] the minimum inhibiting concentration increasing progressively as increasing numbers of organisms are inoculated above 10^4/ml On solid media however similar end points are obtained with undiluted cultures and with the same cultures diluted 1 100 There is also some increase in the minimum inhibiting concentration with prolonged incubation in broth [53] this does not appear to be related to deterioration of the antibiotic but rather is a result of resumption of growth in concentrations that are only bacteriostatic For many strains novobiocin may be bacteriostatic at some concentrations and bactericidal at higher concentrations [8 5 56 93] Thus there may be a rather wide spread between the bacteriostatic and bactericidal concentrations for certain organisms notably various streptococci and especially those of group A but with strains of *Staph aureus* there is usually only a narrow range of concentrations over which partial inhibition occurs [55]

From the clinical point of view and with respect to the determination of novobiocin concentrations in blood and serum the most important problem is the binding of novobiocin to serum protein This binding effect interferes with the action of novobiocin so that the minimum inhibiting concentration for any strain increases as the concentration of serum is increased This inhibitory effect of serum on the action of novobiocin is demonstrable both in broth and in the agar cup plate method and may be very marked For example Martin and co workers[67] found that the minimum concentration of novobiocin in saline producing a zone of inhibition with *M pyogenes* as the test organism was about 0 3 µg /ml as compared with 5 µg /ml of the antibiotic required in serum With *S lutea* as the test strain the lowest concentration producing a definite zone of inhibition was 0 5 µg /ml in saline as compared with 20 µg /ml in undiluted serum In heart infusion broth inoculated with a standard amount of culture of *M aureus* total killing of the culture was effected by a concentration of 0 78 µg /ml whereas 50 µg /ml was required to produce the same effect in half serum and half broth

Diffusion studies through a cellophane membrane showed that novobiocin was bound at least 90 per cent to serum protein Similar results have been reported by many other workers [34 55 64 97] Tennent et al[58] found that 74 per cent of novobiocin was bound in 0 5 per cent solution of crystalline bovine albumin and 30 per cent was bound in 0 05 per cent solution of the same albumin The albumin bound novobiocin could be dialyzed out into fresh buffer showing that the protein binding is reversible

The exact mode of action of novobiocin has not been elucidated There is some evidence that with some gram negative organisms novobiocin inhibits cell division but does not interfere with growth of the cell [83] In such organisms it does not interfere with nucleic acid synthesis (neither ribonucleic acid nor desoxyribose nucleic acid[10]) Marked morphological changes have been ob

served in *Proteus* during exposure to a minimum inhibiting concentration of novobiocin [0] The bactericidal action of this antibiotic is exerted only on actively growing organisms not on organisms in the resting state [3] Intra cellular organisms are apparently protected against the action of many times the minimum inhibiting concentration of novobiocin [89]

RESISTANCE AND CROSS RESISTANCE

As already noted one of the features of greatest interest in novobiocin is that its activity is not related to that of any of the other antibiotics that had been in wide use Strains of staphylococci and of other organisms made resistant in vitro to penicillin streptomycin tetracycline chloramphenicol erythromycin and several other agents show little or no change in susceptibility to novobiocin The reverse is also true that is strains made resistant in vitro to novobiocin by exposure to that agent retain essentially intact, their susceptibility to all other antibiotics with which they have been tested [33 34 60 67 94]

Resistance of staphylococci to novobiocin does however develop quite rapidly after exposure to it in vitro [60 0] and this has occurred although not nearly so rapidly or regularly during treatment of staphylococcal infec tions in patients The rate of increase in resistance in vitro may be quite rapid at first and then proceed at a slower step rate [6] A single exposure of a culture containing 1 million staphylococci per ml results in the emergence of variants 10 to 30 times more resistant than the original strain [1] Other organisms such as pneumococci and many streptococci acquire resistance in vitro less readily Of interest is the observation of Green et al [41] who found that when they increased the resistance to novobiocin of two strains of staphylococci of phage pattern 52/44A by two and three subcultures re spectively the increase in novobiocin resistance was accompanied by a loss of susceptibility to the phages Resistance has also been shown to develop quite readily in tubercle bacilli exposed to novobiocin in vitro [100]

ACTION OF COMBINATIONS OF NOVOBIOCIN WITH OTHER ANTIBIOTICS IN VITRO

The combined action of novobiocin with other antibiotics has been studied by a number of groups of workers and their results have been variously in terpreted depending on the strains tested the methods used and the definitions applied [9] The earliest observations of Wallick et al [94] and of Barbiers and Lewis suggested that substantially greater activity (synergism) resulted from the combination of novobiocin with a number of other active antibiotics

notably penicillin and tetracycline than when one was used alone Chabbert et al[14] observed different effects from the combination of novobiocin with other antibiotics in vitro depending on the strains of *Staphylococcus* tested they used penicillin tetracycline chloramphenicol and erythromycin as the second antibiotic in their tests Rantz et al [3] interpreted some of their findings as suggestive of the possible potentiation or synergism of penicillin with novobiocin in a few strains of staphylococci that were resistant to both agents *separately*

Jawetz et al [51] however did not observe any true synergism in the sense of *increasing* the early bactericidal rate as compared with that of the more active individual component except in occasional strains exposed to the com binations of novobiocin with either bacitracin or neomycin In such instances they considered that the combined action of the antibiotics was essentially unilateral namely the prevention of emergence of novobiocin resistant mu tants by the bacitracin or neomycin rather than by mutual protection. When they used a penicillinase producing *Staphylococcus* that was resistant to 20 μg /ml of streptomycin they could demonstrate no combined action of novo biocin with either penicillin or streptomycin

Johnson et al[5] *showed that novobiocin did not interfere with the action* of a sulfonamide (sulfamethylthiadiazole) on novobiocin resistant organisms such as *A aerogenes* and *Pseudomonas aeruginosa* which are generally asso ciated with urinary tract infections

Jones and Finland [4] showed that novobiocin and penicillin when they were given in equal amounts produced antibacterial activity of serum against certain standard test strains that was only intermediate between those of the individual antibiotics There was no evidence of any synergistic action of these antibiotics against the strains used but there was a suggestion of some reduced activity of novobiocin by penicillin against a strain of *Staphylococcus* that was highly resistant to penicillin

Repeated exposures of staphylococci to a combination of increasing con centrations of novobiocin with a constant amount of a weakly bacteriostatic agent such as sulfisoxazole or with other antibiotics against which the *Staphy lococcus* was initially insensitive failed to inhibit the development of novo biocin resistance [6] When however novobiocin was combined in a fixed ratio with other effective antibiotics notably penicillin or tetracycline to which the staphylococci were originally sensitive the emergence of resistant variants during successive subcultures was markedly delayed and depressed as com pared with the resistance that developed to the same agents when used in dividually [5] Lowbury[63] studied five strains of *Staph aureus* that were orig inally sensitive to both novobiocin and erythromycin he found that they acquired resistance more rapidly when grown in media containing either antibiotic alone than they did in the presence of a mixture of the two

EFFECT OF NOVOBIOCIN IN EXPERIMENTAL INFECTIONS

Novobiocin given either orally subcutaneously or intramuscularly has been shown by several groups of workers to be active against intraperitoneal infections of mice with staphylococci streptococci pneumococci *Pasteurella* and several strains of *Proteus* [33 93 97] Interestingly enough some of the latter organisms were only moderately susceptible to the antibiotic in vitro The antibiotic has not proved effective in mice against other coliforms salmonellae shigellae or *Pseudomonas* In appropriate experimental hosts novobiocin is usually ineffective against infections with tubercle bacilli fungi protozoa viruses or rickettsiae It has shown some activity against the cutaneous infection of rabbits with *Treponema pallidum*[36] and showed some protection of mice against pulmonary infection with *H pertussis* [93]

Eigelsbach et al [7] found novobiocin to be very effective in vitro and in mice against infection with strains of *Bacterium tularense* including two variants one resistant to streptomycin and the other to chloramphenicol and tetracycline Dutta and Colah found novobiocin to be bacteriostatic and bactericidal against *Vibrio cholerae* in concentrations of 5 and 10 μg/ml respectively They used novobiocin in the treatment of an experimental cholera infection of rabbits and obtained 86 per cent survivors when treatment was begun as late as 16 hours after infection of the animals Yegian and Budd[100] showed that novobiocin exerts slight to moderate activity against experimental tuberculosis in guinea pigs However resistance to novobiocin developed quite readily in tubercle bacilli exposed to novobiocin in vitro They found that the atypical and saprophytic mycobacteria which they studied were highly resistant to novobiocin and consequently suggested that this antibiotic might profitably be used to help differentiate these strains from tubercle bacilli

Several studies have been reported on the effect of novobiocin on the intravenous infection of mice with virulent strains of *Staph aureus* These have shown that novobiocin prevents death in mice promotes healing of renal lesions and causes a marked reduction in the number of staphylococci that can be cultured from the organs especially from the kidneys of treated mice as compared with untreated controls Of interest is the fact that staphylococci cultured from the kidneys of mice after prolonged treatment with novobiocin retain their original susceptibility to that antibiotic This indicates that the failure to remove all of the staphylococci from the kidneys is not the result of the development of resistance it has been suggested that this may be due to low levels of the drug available to the surviving organisms[14] or to the persistors but it is more likely to be due to the intracellular or other protective sites of the surviving bacteria that keep them from contact with adequate concentrations of antibiotic

In one study[5] it was shown that treatment with various dosages of the combination of penicillin plus novobiocin produced a much greater percentage of survivors among mice infected with *Staph aureus D pneumoniae* or *Streptococcus hemolyticus* than treatment with either antibiotic alone given in the same dosage McCune et al [6] using the intravenous staphylococcal infection of mice showed that the combination of novobiocin plus streptomycin was more effective in reducing the number of staphylococci in the kidney than either novobiocin or penicillin given alone or the combination of the two, but staphylococci survived in the kidney under all of these treatments

TOXICITY AND PHARMACOLOGY IN ANIMALS

Novobiocin has a very low acute toxicity for mice by oral intraperitoneal intravenous or subcutaneous routes [8, 67, 75] In the guinea pig single or multiple subcutaneous or intraperitoneal dosages are less well tolerated this being reminiscent of the toxicity of penicillin for the guinea pig In mice rats and dogs rather large oral dosages given over prolonged periods are well tolerated Isotonic solutions (130 mg /ml) however have proved irritating to the veins in dogs Novobiocin is also irritating when given subcutaneously or intramuscularly in rabbits [8] In dogs large intravenous dosages produce serious changes in the liver gastrointestinal tract and kidneys with perivascular hemorrhages and edema [8] In these animals Robinson and Silber[74] observed a yellow discoloration of the plasma during oral administration this was noted three hours after single oral doses of 100 mg /Kg reached its peak in 12 hours and cleared in 18 hours This color gave negative tests for bile and was removed by extraction with neutral ethyl acetate a procedure that does not remove the yellow color of the plasma of truly jaundiced rats it was therefore considered to be a metabolic product of novobiocin Rats given large doses of novobiocin for 90 days developed a mild yellow discoloration of the plasma skin and visceral fat with large dosages (1 2 Gm /Kg.) they lost weight rapidly Forty per cent of the animals died after five days and showed foci of necrosis in the liver cell cords Novobiocin produced no important pharmacodynamic effects [58] However large single doses given intravenously to dogs produced detectable hemoglobinemia for four hours repeated small doses produced only minimal hemolysis

ABSORPTION EXCRETION AND DISTRIBUTION IN THE BODY

This aspect has been studied by many workers in animals and man [6, 1, 42, 56, 58, 60, 61, 64, 67, 69, 1, 8, 81, 84, 87, 93, 9, 99] Both in mice and in dogs novobiocin is well absorbed when given orally and the antibiotic can be found in varying concentrations in almost all body fluids and tissues except in cerebrospinal fluid only minimal concentrations have been found in the brain The antibiotic

is excreted into the bile in large concentrations after a few doses have been given and the bile may contain much higher concentrations than the plasma The antibiotic is also well absorbed from intramuscular injections but to date nonirritating preparations have not become available In mice there is a marked parallelism between the blood level curves after the same single dose given orally intramuscularly and intravenously, suggesting complete or almost complete absorption from the oral route [93]

Maximum concentrations are achieved in the blood within two or three hours after an oral dose both in dogs and in man, and the levels are fairly well sustained for several hours These levels vary almost directly in proportion to the dose [6, 99] There is some cumulation of the antibiotic in the blood during the first few doses but the levels soon stabilize so that there are only minor fluctuations in blood levels when oral doses are given every six or eight hours in the usual dosage range and even every 12 hours with somewhat larger dosages Initial doses appear to be absorbed better from an empty stomach than after a meal [81, 87] the peak levels being higher and achieved earlier when the antibiotic is taken in the fasting state Although fairly high concentrations are found in the urine generally several times as high as those found in the blood during administration of repeated doses only about 3 per cent of an administered dose can be accounted for in the urine [81, 84, 99] Considerable amounts however are found in the feces of man and dogs suggesting that in these animals some of the orally administered antibiotic may not be fully absorbed [67, 68] However some of the fecal antibiotic undoubtedly represents in part at least novobiocin that has been absorbed and excreted into the bile

Blood levels achieved in both adults and children are much higher with novobiocin than with any of the antibiotics now in general use These concentrations may be many times those required to inhibit susceptible organisms *in vitro* In man the antibiotic has been demonstrated in pleural, ascitic and joint fluids, usually in lower concentrations than in the blood but it has not been demonstrated in cerebrospinal fluid except in very low concentrations in 1 patient with meningitis [6, 21, 61, 64, 67, 68, 81]

CLINICAL USES OF NOVOBIOCIN

As might be expected with any new antibiotic the bulk of the early reports on the use of novobiocin have been difficult to interpret because of the variability in choice of cases the type of data made available the criteria used for evaluation and the paucity of controls for comparisons either with untreated cases or with patients treated with other effective antibiotics In general the largest number of favorable reports have dealt with staphylococcal infections particularly those that had failed to respond to treatment with other common antibiotics because of resistance of the offending *Staphylo-*

coccus Favorable responses have also been reported in infections due to other gram positive bacteria and in certain cases of urinary tract infections due to gram negative bacilli notably *Proteus* infections these results on the whole have been comparable with although often somewhat less favorable than, the brilliant effects one had been accustomed to expect from the earlier successful antibiotics when the causative organisms were highly susceptible to them Moreover many of the reports and particularly the more recent ones have been confused by the use of combinations of novobiocin with other antibacterial agents notably penicillin and tetracycline so that the true contribution of the novobiocin to the results has become even more difficult to delineate

Novobiocin has generally been administered orally as the monosodium salt in capsules or as the calcium salt suspended in sirup Intramuscular preparations have been used experimentally but have thus far proved too irritating for general use An intravenous form is available that is prepared by adding 5 ml of a sterile 10 per cent solution of N N-dimethylacetamide to a vial containing 500 mg of sterile novobiocin this in turn is added to 500 to 1000 ml of isotonic saline and administered by intravenous drip Such a preparation* has given favorable results similar to those obtained with oral preparations and could be used when oral therapy is not well tolerated [35]

Another injectable form of sodium novobiocin is available † which may be given either intravenously or intramuscularly but not intrathecally The manufacturer supplies the following instructions for the use of this preparation

For intravenous infusion 500 mg is dissolved in 250 to 500 ml of sodium chloride injection U S P or it may be given intravenously by syringe injection using 500 mg dissolved in 50 ml of sodium chloride injection U S P The usual technique and precautions for an intravenous injection should be observed slow injection being recommended For intramuscular injection 500 mg is dissolved in 2 5 or 5 0 ml of either sodium chloride injection U S P or water for injection U S P the reconstituted solution should be injected deep intramuscularly the dose may be divided and injected in two sites to reduce pain The reconstituted solution should be used immediately if the solution is cloudy it should be discarded It is emphasized that only sodium chloride injection U S P be used for intravenous infusion or injection and only sodium chloride injection U S P or water for injection U S P be used for the intramuscular injection Other solutions particularly those with a *p*H of 6 or less should not be mixed with the novobiocin solution since the free acid of novobiocin may precipitate

---

The trade name of The Upjohn Co for an intravenous form of novobiocin is Mix-O-Vial Albamycin

† The trade name of Merck Sharp & Dohme division of Merck & Co Inc for the injectable form of sodium novobiocin is Lyovac Cathomycin sodium

Novobiocin has been used more extensively in the treatment of staphylococcal infections than for infections due to any other bacteria It has proved to be one of the most effective of the agents available for severe staphylococcal infections because nearly all of the causative organisms have been found to be highly susceptible For example Pulaski and Isokane[72] tested strains of *Staph aureus* with 5 μg discs of novobiocin and found 98 2 per cent of 116 strains isolated from wound exudates and 99 of 100 strains from nasal cultures to be susceptible a large proportion of these strains were resistant to other commonly used antibiotics In 106 patients with a large variety of pyogenic surgical infections whom they treated with novobiocin 74 per cent gave favorable results that were comparable to those obtained with other effective antibiotics They used 1 5 to 2 0 Gm daily in severe cases and 1 0 Gm daily in milder cases

Favorable results have frequently been registered with the use of novobiocin alone but most often they were obtained with combinations including other antibiotics or when novobiocin was added to treatment with other agents to which the offending organisms were at least moderately susceptible The use of novobiocin particularly alone or when given together with other antibiotics to which the *Staphylococcus* is not susceptible has been complicated by the development of novobiocin resistance in the *Staphylococcus* during treatment when that has occurred it has usually rendered further treatment ineffective or resulted in relapse or extension of the infection after varying degrees of improvement had been achieved In a report by Chabbert et al[13] only 1 of 4 patients with staphylococcal septicemia and pulmonary localization had a completely favorable result with novobiocin therapy in the other 3 relapse occurred and the development of novobiocin resistance was shown to be the cause

The nature of the staphylococcal lesions with their tendency to suppurate and encapsulate renders difficult the penetration of the antibiotic to the offending organisms and requires long periods of treatment in order to obtain favorable results that are lasting Such prolonged treatment has often been impossible to complete because of sensitization reactions to the drug which have required its discontinuance These two factors the development of novobiocin resistance in the *Staphylococcus* and of sensitization of the patient to the antibiotic have largely limited the possibility of realizing the full therapeutic potential of this agent in staphylococcal infections Nevertheless rapid improvement with arrest of spreading lesions cessation of bacteremia and reduction in toxemia has been sufficiently striking to consider that this agent has proved lifesaving in many seemingly fulminant or rapidly progressing cases even though it has often been necessary to resort to other agents to complete the bacteriological and clinical cure

Surgical drainage of surface lesions and of other accessible foci has often

been an equally important factor and at times the determining one in the improvement of the patient when large purulent foci have developed In such cases novobiocin has served to reduce the extent of the surgery required and has often limited the size of the lesions needing drainage or the use of the antibiotic has rendered such drainage unnecessary if treatment was undertaken before the suppuration developed

The types of staphylococcal infections that have been favorably affected have varied in location number and severity They have included pyodermas and infected dermatoses of which the great majority are reported as having yielded excellent or good responses to novobiocin Infections of skeletal or soft tissues wound infections and abscesses and some cases of osteomyelitis have in most instances responded favorably at least when the antibiotic was first administered Occasional cures of cases of staphylococcal endocarditis and of severe and extensive staphylococcal pneumonias have been recorded but in these cases other antibiotics were employed in addition although the novobiocin appeared to increase the degree and rate of improvement Actually only a few instances have been recorded of complete clinical and bacteriological cures in patients with staphylococcal endocarditis or with extensive or multiple suppurative lesions or in late and severe cases without resort to such additional treatment with other antibiotics to which the causative organisms were also sensitive or without surgical drainage of the extensive suppurative lesions

Novobiocin does not penetrate into the cerebrospinal fluid but it has been used topically with success in some cases of staphylococcal meningitis Giusti and Mori[38] gave daily dosages of 10 to 40 mg of novobiocin by the ventricular lumbar or intracisternal routes as a supplement to oral therapy to 6 patients with staphylococcal meningitis in 4 of whom this was a complication of tuberculous meningitis Combined with other antibiotics the novobiocin produced a complete remission of the disease within six to eight days and without side effects or sequelae

Novobiocin has been used successfully to reduce the number of staphylococci in the bowel of patients with postoperative diarrhea but it has had no effect in such diarrheas when a normal flora was present in addition to the staphylococci As a preoperative bowel preparation however Cohn and Longacre[16] found novobiocin alone to be unsatisfactory although it was highly effective in combination with neomycin Similar findings were reported by Shidlovsky et al [9] In severe staphylococcal enterocolitis where the *Staphylococcus* is the only or predominant organism novobiocin has been employed with eminent success It has little or no effect on the normal bowel flora particularly on the gram negative bacteria that constitute the bulk of that flora and hence is not likely to give rise to staphylococcal enterocolitis[30] Nevertheless at least 1 case has been reported[3] in which this postoperative

complication occurred within one day after novobiocin was started although the author expressed conviction that the novobiocin caused this diarrhea the evidence presented does not support this conclusion

Novobiocin has produced favorable results in the treatment of pneumococcal pneumonias[18, 50, 60, 71, 91] and in the treatment of hemolytic streptococcal infections [6, 61, 71] of the upper respiratory tract It has also been used with favorable results to treat cases of streptococcal cellulitis Although excellent results were recorded especially in pneumococcal pneumonia the response of such patients in general has been considered by some authors [1] to be not quite so striking either bacteriologically or clinically as that generally observed when penicillin is used in similar cases that are caused by penicillin sensitive organisms Failure in 1 of 3 cases of pneumonia was shown to be associated with development of resistant pneumococci [91]

Tall et al[60] treated 16 hospitalized scarlet fever patients for three or four days with novobiocin 40 mg/Kg daily in four divided doses after which they gave penicillin routinely The novobiocin treated patients had an unsatisfactory clinical response as manifested by persistence of fever and this was also associated with persistence of β hemolytic streptococci in cultures of the throat of 10 of the 16 patients throughout the three or four days of novobiocin therapy in spite of adequate serum levels (greater than 64 μg/ml) in all patients However there was no change in the susceptibility of the streptococci to novobiocin during the treatment Similar unfavorable responses both clinical and bacteriological were reported by Breese et al[8] in streptococcal infections in children

Although strains of *H influenzae* and *H pertussis* are quite sensitive to novobiocin in vitro very few cases of infection with these organisms have been reported Because of the poor penetration of novobiocin into the cerebrospinal fluid there has been a reluctance to treat cases of influenzal meningitis as these would not be expected to respond favorably

Excellent results without relapses were reported by Gost[40] in 20 unselected cases of undulant fever all of which were proved by isolation of organisms from the blood The author claims that he had never seen such favorable effects with any other agent In an attempt to verify these results Debono [4] failed to get responses with novobiocin that were either as constant or as dramatic as with tetracycline of 15 patients whom he treated for 15 days 5 relapsed with positive blood cultures within four months and 7 got incomplete effects with relapses occurring in 4 of them within two months

The results of treatment of 27 men for acute gonorrheal urethritis as reported by Willcox [98] indicate that novobiocin given orally in a dosage of 2 to 3 Gm was inadequate to effect a cure this amount has usually been successful in similar cases treated with several other antibiotics Even dosages of 8 or 10 Gm of novobiocin given over a period of two days gave only 66 to

78 per cent cures Novobiocin was therefore considered by this author as not very useful in the treatment of acute gonorrhea In the treatment of 3 cases of early syphilis Edelson [6] found novobiocin given intravenously to be unsuccessful although there was apparent early improvement and no untoward reactions resulted from the injections Withdrawal of the drug permitted a prompt exacerbation that was easily controlled with penicillin

Because a considerable proportion of strains of *Proteus* and a smaller number of those of *E coli* are susceptible to novobiocin in concentrations that are readily achievable in the urine this antibiotic has been used in the treatment of a sizable number of cases of various urinary tract infections Herrold [43] for example considered novobiocin to be useful in the treatment of urinary tract infections caused by gram positive coccal organisms and by *Proteus* Seneca et al [77] in a study of 60 cases of urinary tract infections found novobiocin to be effective in many infections with *Staph aureus* *Proteus* and *Str faecalis* and even in some with *E coli* and *Ps aeruginosa* In vitro resistance appeared to increase rapidly in many of these cases and the authors suggested that novobiocin be used in combination with other drugs such as tetracycline rather than alone

However only a minority of such urinary infections in chronic cases have shown a favorable response that could be attributed to the antibiotic Hughes et al [48] for example reported 21 failures among 26 patients with chronic urinary tract infections treated with novobiocin 250 mg four times daily for 7 to 14 days Only 1 of 9 patients in whom *Proteus* was the offending organism responded favorably to this treatment Both bacteriologically and clinically enterococcal infections have failed to respond in most instances [69] The few successes have been mostly in infections with the more susceptible strains of *Proteus* but even some infections with *E coli* have occasionally responded in such a manner as to suggest that the antibiotic may have been of some help Such cases however are difficult to evaluate particularly when the organisms obtained before treatment were insensitive to the antibiotic in vitro Acidification of the urine before and throughout treatment as suggested by Nichols and Finland [69] may be of help in view of the greater activity of novobiocin in an acid medium

The majority of the more recent clinical reports have dealt with the use of novobiocin in mixtures with either penicillin or tetracycline or sulfonamides [2 11 2 9 39 0] In none of these reports have adequate data been presented from which the respective roles of novobiocin and the other constituents of the mixture could be evaluated Most though not all of these reports have dealt with minor surgical infections or with pyodermas and infected dermatoses As with most such reports regardless of the agents under investigation the results have almost always been reported as excellent or favorable without critical evaluation of the data and without attempt to incorporate proper

control studies A large proportion of the cases are such that they could hardly be considered suitable for treatment with any antibiotics by most physicians and certainly are not suitable for comparative evaluation of therapeutic agents including the same agents individually

There appears to be a more or less direct relation between the susceptibility of the causative organisms and the favorable responses that have been reported although the data are not always adequate for reliable correlations This is well illustrated in a study carried out by Tunevall[90] in which he made serial cultures of tracheal secretions from tracheotomized patients He found that staphylococci that were sensitive to 2 μg or less of novobiocin per ml were eliminated by novobiocin treatment whereas other bacteria that were sensitive to 4 μg /ml or more resisted this treatment and could not be eliminated in spite of serum concentrations of 15 to 20 μg of novobiocin per ml for five days

Most of the clinicians who carried out the early trials and who have continued to study the patients they have been treating with this antibiotic have been impressed with novobiocin as an active and useful agent particularly in infections with staphylococci that are resistant to the other generally available antibiotics However due to the tendency of organisms particularly staphylococci, to increase in resistance during treatment and because of the relatively frequent occurrence of drug rashes from its use they have felt that novobiocin is best reserved for use in infections with organisms susceptible to this agent but resistant to others or in patients in whom the other effective agents such as penicillin are not well tolerated In such cases novobiocin is best used along with another antibiotic to which the organisms are sensitive

UNTOWARD EFFECTS

On the whole novobiocin appears to be well tolerated when it is given orally, serious reactions have been remarkably few except for the unusually frequent occurrence of rashes attributed to this antibiotic However the incidence of side reactions reported by different observers has varied markedly most of the discrepancies probably being the result of inclusion of minor symptoms or the recording of unexpected or unexplained variations in the reports of certain laboratory findings without reference to other possible causes of these aberrations No significant untoward effects have been noted by any of the investigators who were studying the effects of single doses beyond some local irritation at the site of local intramuscular injections

In a review of the untoward reactions recorded in reports of more than 1300 patients[31] the most frequent complication of novobiocin therapy was found to be the skin reactions These were recorded as occurring in about 7 per cent of all the patients but in some of the individual reports a higher incidence—up to more than 20 per cent—of skin rashes has been observed

For example Breese et al[8] observed rashes in two thirds of 24 patients who were treated with novobiocin for streptococcal infections and in 14 of 19 patients who had received the antibiotic for five days or longer

It is quite clear from some of the reports that a significant proportion of the skin reactions were caused by other agents that had been given just prior to starting novobiocin penicillin was probably the most frequent cause of such reactions particularly those of the urticarial or serum sickness type which appeared within the first four or five days after novobiocin was started or soon after treatment with the combination of penicillin and novobiocin was begun The combination of novobiocin and tetracycline has rarely given rise to such reactions during the first few days of treatment

The characteristic rash occurring during treatment with novobiocin alone and which is probably the result of sensitization to that antibiotic is a generalized morbilliform eruption or a diffuse scarlatiniform erythema involving the trunk face and extremities and appearing between the sixth and twelfth days of novobiocin administration in dosages of 1 5 Gm /day or more in more than 4 out of 5 cases for which the time of onset is available the rash first appeared at that time Fever has been noted to accompany the rash in only about one fourth of the cases and it was more frequent in the urticarial reactions in which penicillin may have been implicated Urticarial rashes have been noted however in occasional patients who had not received penicillin and pruritus regularly accompanied the urticarial reactions but was not regularly mentioned in the patients with the morbilliform or scarlatiniform eruptions The rash and fever have usually subsided within two to four days after novobiocin was discontinued

Readministration of the antibiotic to patients who had rashes during novobiocin treatment has resulted in reproduction of the rash in less than one half of those in whom this was attempted but some of the cases in which this was done or in which the rash cleared during continued administration of novobiocin were undoubtedly reactions to other substances and in a few of these cases this was actually shown to be the case by readministration of the other probable offender The results of skin tests with novobiocin are also subject to similar errors and to other difficulties in interpretation in addition to the well known problems involved in using skin tests for determining sensitivity to drugs Many of the drug reactions have been treated with antihistaminics or with adrenocortical hormones but this may reflect the enthusiasm of the physicians for their use and could not necessarily be considered an indication of the severity of these reactions indeed some of these reactions to novobiocin occurred and persisted during the administration of these agents for other indications Some of the skin reactions especially those in persons with a history of other allergic tendencies may be serious and may be followed by other severe manifestations of drug toxicity if treatment is continued espe

cially in patients with fever On the other hand some of the mild erythemas that occurred after a week or 10 days of novobiocin therapy have in many patients subsided without interrupting the treatment when the course of the infection required it

Hughes[49] reported the case of a 7 year old child who had previously been treated with novobiocin without ill effects On the second administration of this antibiotic he was given 125 mg orally three times daily and developed a severe allergic reaction with skin lesions resembling those of the Stevens Johnson syndrome This was accompanied by nuchal rigidity marked irritability stupor pleocytosis of the cerebrospinal fluid with negative bacteriological and viral studies All the symptoms responded well to treatment with adrenal steroids

Gastrointestinal symptoms have also been reported with varying frequency by different observers many of whom may have failed to appreciate or to take into account the presence of these symptoms at the time treatment with novobiocin was undertaken In many indeed in most cases continuation of novobiocin therapy has been possible without aggravating these symptoms or with actual subsidence of the evidence of gastrointestinal irritation Nausea epigastric distress and occasionally vomiting have been recorded in about 1 5 per cent of the patients treated with novobiocin and in most of the cases these reactions have been mild and transient Diarrhea has been specifically recorded as caused by the antibiotic in about 1 per cent of patients but only rarely has this been severe enough to interfere with continued therapy Loose and bulky stools with mild abdominal discomfort were noted in about 6 per cent of cases but had not constituted much of a problem in fact nearly all the cases with these symptoms were recorded by only two groups of authors[18, 95] Monilial infections or the appearance of large numbers of yeasts or fungi in the feces has rarely been reported as a complication of novobiocin therapy

Leukopenia has been noted in a few patients but this has been of little or no significance except that it was disturbing to the physicians when first observed In most instances the leukopenia occurred early in the course of treatment accompanied favorable clinical responses to the antibiotic and the blood counts rose while the novobiocin was being continued moreover the proportion of neutrophils did not drop to very low levels Such effects have frequently been noted in the past during treatment with other effective antimicrobial agents ever since the introduction of active sulfonamide drugs In only 1 patient among the 1300 collected was a marked drop in leukocytes accompanied by a suppression of the granulocytes and in this case the effect was subsequently reproduced by readministration of novobiocin[71]

Simon and Rogers[6] reported a case in which agranulocytosis developed along with a rash during treatment with novobiocin and tripelennamine hydrochloride although they could not establish the identity of the offending agent

they considered novobiocin to be responsible In another case Colville and co workers[17] reported finding thrombocytopenia and granulocytopenia accom panying a rash that developed after 11 days of treatment of a patient with staphylococcal septicemia Day et al [3] also reported a case in which throm bocytopenia accompanied the development of a pruritic morbilliform eruption during novobiocin therapy this was shown to be related to the development of platelet lysins in the serum and plasma and other evidence of poor platelet function

The significance of the eosinophilia recorded in about 1 2 per cent of the novobiocin treated cases and which probably occurred more frequ ntly is difficult to assess In some patients it was obviously related to the allergic response and accompanied a skin reaction in others it occurred early and may have been a response to some previously administered agents—most often either penicillin or streptomycin or both whereas in others it may have been a common sequel accompanying the recovery phase of the infection itself Anemia attributable to novobiocin was not reported in any of the cases

An elevated icterus index and indirect serum bilirubin level was noted in only a few patients and in these this finding was not accompanied by other evidence of impaired liver function In view of the observation of Robinson and Silber [74] it is surprising that this yellow color of the skin and serum has not been observed more often As in the experimental animals this was prob ably related to an abnormal pigment metabolite of novobiocin in the blood but this was not definitely proved in any of the patients Moreover the time of its reported appearance varied from the second day to after the second week of treatment and in some patients it lasted only two or three days in spite of continuing the treatment while in others it persisted for more than 10 days after a brief course of treatment with novobiocin Bridges et al[9] reported the case of a boy of 14 who in the course of treatment with various agents for juvenile rheumatoid arthritis also received novobiocin 2 Gm orally twice a day for eight days because of the report of positive blood cul tures for some unusual *Streptococcus* which was sensitive to this antibiotic On the sixth day of this treatment he developed jaundice and a pruritic skin rash His condition worsened in spite of cortisone therapy and he died Autopsy showed acute diffuse hepatic necrosis and generalized lymphoid hyperplasia which the authors thought could be properly attributed to the novobiocin therapy

Impairment of renal function was not observed in any of the reported cases and the only abnormal urinary finding was transient microscopic hematuria noted as accompanying the rash and fever in 2 instances

COMMENT

Nearly all of the groups of workers who have investigated the clinical

effects of novobiocin have been more or less uniform in their judgment as to the place of novobiocin as an antibacterial agent There is general agreement that novobiocin is an effective agent and that it is clearly indicated in the treatment of serious staphylococcal infections when other antibiotics have failed or could be expected to fail due to the resistance of the infecting strains to those agents It could also be recommended in certain other infections with susceptible organisms when other effective antibiotics are contraindicated due to hypersensitivity of the patient or when the infection fails to respond to an adequate dosage of those antibiotics Most of these investigators and other responsible persons have favored limitation of the use of novobiocin to such cases in order to avoid as far as possible the emergence and spread of novobiocin resistant staphylococci which can clearly be anticipated to result from its widespread and indiscriminate use Moreover the frequent occurrence of skin reactions from its use also justifies this limitation

Novobiocin cannot be recommended as the antibiotic of choice for the treatment of pneumococcal or hemolytic streptococcal infections in spite of the fact that most of the former seem to respond favorably Other less toxic drugs such as penicillin erythromycin or the tetracyclines may be expected to produce equally favorable and usually better results the same is true with gonococcal infections

Most observers who have encountered the development of novobiocin resistant strains of staphylococci during treatment with novobiocin have also recommended that this antibiotic never be used alone for the treatment of staphylococcal infections but that some other agent to which the organism is also at least moderately susceptible be given together with the novobiocin at all times Thus far there is still too little information available as to the effects of such use on the emergence of resistant staphylococci during treatment The data presented by Lepper et al [9] suggest that such combined treatment is only partially and temporarily effective The particular combination chosen by these workers namely novobiocin plus spiramycin is not an optimum one since spiramycin by itself has relatively low antistaphylococcal activity as compared with erythromycin and shows marked cross resistance with the latter Also there was significant residuum of erythromycin resistant staphylococci in the hospital where their study was carried out A more recent report of the use of antibiotic combinations by Barber et al[4] suggests that the combination of erythromycin and novobiocin may be more promising since erythromycin resistant strains did not result from the use of this combination in 108 cases but novobiocin resistant strains emerged in 2 of their cases

In another trial of the use of novobiocin in combination with erythromycin in the prophylaxis and treatment of infection in patients with burns Lowbury[63] reported that Staph aureus was cleared from a higher proportion of covered burns that were treated with these two antibiotics together (68 per cent)

than from comparable burns receiving no chemotherapy (10 per cent) Also the therapeutic effect of this mixture was significantly greater than that of erythromycin used alone and also greater than that of novobiocin used alone in a small series of burns Patients treated by the exposure method did not usually lose the staphylococci during treatment with novobiocin plus erythro mycin (or possibly continued to become reinfected) This author found no evidence of synergistic action of novobiocin with penicillin against staphylo cocci in vitro The incidence of erythromycin resistant staphylococci fell dur ing the first four weeks of a period when novobiocin and erythromycin were used only in combination minor degrees of resistance to novobiocin began to appear in the second week and there was a gradual increase in the number of staphylococci resistant to erythromycin and slightly resistant to novobiocin from the fifth week on Resistance to novobiocin first appeared in the patients treated by the exposure method

There is an apparent paradox in the suggestions that on the one hand the use of novobiocin be limited to infections with organisms resistant to other antibiotics and on the other hand it be used only in combinations with other antibiotics to which the organism is susceptible However the use of novobiocin together with another antibiotic to which the *Staphylococcus* is already highly resistant cannot be expected to provide any additive or synergistic effect nor can any protection against the development of novobiocin resistance be ex pected It is essential in order to avoid or delay the emergence of resistance that both components of the combinations be active and used simultaneously This statement is based on clinical experience with novobiocin and with other antibiotics like streptomycin and erythromycin that have a similar tendency to produce resistant variants when used alone To be sure Barbiers and Lewis[5] have reported some synergistic effect of novobiocin plus penicillin against both penicillin-sensitive and penicillin resistant strains of *Staph aureus Proteus vulgaris* and *Proteus rettgeri* in mice and they also found this combina tion to be superior in infections of mice with *Str hemolyticus* and *D pneumoniae* in spite of the fact that this combination was not so good in vitro Rantz et al [3] also reported some suggestive in vitro potentiation or synergism of penicillin with novobiocin in a few strains that were resistant to both agents separately It is very doubtful however if such combined effects ever come into play in the treatment of penicillin resistant *Staphylococcus* infection in patients on the other hand the reverse is often true that resistance to novobiocin develops in spite of the use of large dosages of penicillin when the offending organism is a highly resistant penicillinase producing *Staphylococcus*

In this connection it is of interest that Caswell et al [12] in a study of 158 hospital strains of staphylococci isolated mostly in 1956 found practically all of them to be sensitive to novobiocin chloramphenicol neomycin and

effects of novobiocin have been more or less uniform in their judgment as to the place of novobiocin as an antibacterial agent There is general agreement that novobiocin is an effective agent and that it is clearly indicated in the treatment of serious staphylococcal infections when other antibiotics have failed or could be expected to fail due to the resistance of the infecting strains to those agents It could also be recommended in certain other infections with susceptible organisms when other effective antibiotics are contraindicated due to hypersensitivity of the patient or when the infection fails to respond to an adequate dosage of those antibiotics Most of these investigators and other responsible persons have favored limitation of the use of novobiocin to such cases in order to avoid as far as possible the emergence and spread of novobiocin resistant staphylococci which can clearly be anticipated to result from its widespread and indiscriminate use Moreover the frequent occurrence of skin reactions from its use also justifies this limitation

Novobiocin cannot be recommended as the antibiotic of choice for the treatment of pneumococcal or hemolytic streptococcal infections in spite of the fact that most of the former seem to respond favorably Other less toxic drugs such as penicillin erythromycin or the tetracyclines may be expected to produce equally favorable and usually better results the same is true with gonococcal infections

Most observers who have encountered the development of novobiocin resistant strains of staphylococci during treatment with novobiocin have also recommended that this antibiotic never be used alone for the treatment of staphylococcal infections but that some other agent to which the organism is also at least moderately susceptible be given together with the novobiocin at all times Thus far there is still too little information available as to the effects of such use on the emergence of resistant staphylococci during treatment The data presented by Lepper et al [9] suggest that such combined treatment is only partially and temporarily effective The particular combination chosen by these workers namely novobiocin plus spiramycin is not an optimum one since spiramycin by itself has relatively low antistaphylococcal activity as compared with erythromycin and shows marked cross resistance with the latter Also there was significant residuum of erythromycin resistant staphylococci in the hospital where their study was carried out A more recent report of the use of antibiotic combinations by Barber et al[4] suggests that the combination of erythromycin and novobiocin may be more promising since erythromycin resistant strains did not result from the use of this combination in 108 cases but novobiocin resistant strains emerged in 2 of their cases

In another trial of the use of novobiocin in combination with erythromycin in the prophylaxis and treatment of infection in patients with burns Lowbury[63] reported that *Staph aureus* was cleared from a higher proportion of covered burns that were treated with these two antibiotics together (68 per cent)

6 BAYNE G M STRICKLAND S C GYLFE, J M AND BOGER W P Novobiocin a study of plasma and spinal fluid concentrations in man Antib Med 2 166–172 1956
7 BOXER, G E AND SHONK, C E. A colorimetric determination of novobiocin in serum or plasma Antib & Chemo 6 589–597 1956
8 BREESE B B DISNEY F A AND TALPEY W B Novobiocin in the treatment of beta hemolytic streptococcal infections in children AM&CT 4 347–351 1957
9 BRIDGES R A BERENDES H AND GOOD R A Serious reactions to novobiocin J Pediat 50 579–585 1957
10 BROCK, T A Studies on the mode of action of novobiocin J Bact 72 320–323 1956
11 CARTER, C H Clinical evaluation of a novobiocin sulfonamide combination in treatment of common infections AM&CT 5 517–520 1958
12 CASWELL H T SCHRECK K. M BURNETT W E CARRINGTON E R LEARNER N STEEL H H TYSON R R AND WRIGHT W C Bacteriologic and clinical experiences and the methods of control of hospital infections due to antibiotic resistant staphylococci Surg Gynec & Obst 106 1–10 1958
13 CHABBERT Y BERROD J HENOCH H AND DUMAS J Antistaphylococcic activity of novobiocin Presse med 66 809–812 1958
14 CHABBERT Y BOYER F SAVIARD M BOULINGRE H AND HERVE, J Determination de l action bactéricide in vivo des antibiotiques dans la staphylococcie rénale de la souris Ann Inst Pasteur 92 760–777 1957
15 CHAIET L AND WOLF F J Antibiotic salts of novobiocin Antib & Chemo 7 231–234 1957
16 COHN I JR AND LONGACRE A B Novobiocin and novobiocin neomycin for intestinal antisepsis Ann Surg 146 184–189 1957
17 COLVILLE J M GALE H H COX F AND QUINN E L Clinical observations on the use of novobiocin in penicillin resistant staphylococcal septicemia In Antibiotics Annual 1957–1958 New York Medical Encyclopedia Inc 1958 pp 920–926
18 COOK, E EASTMAN G AND BUNN P The use of novobiocin in the management of acute pneumococcal and staphylococcal infections In Antibiotics Annual 1956–1957 New York Medical Encyclopedia Inc 1957 pp 396–401
19 COOPER M L. AND KELLER H M Severe staphylococcal infections in young children the isolation of Micrococcus pyogenes var aureus with a specific bacteriophage pattern Am J Dis Child 95 245–252 1958
20 COPPO A The in vitro antibiotic activity of novobiocin on M pyogenes and some intestinal gram negative bacteria Antib & Chemo 7 297–305 1957
21 CORBIN E. E. AND PRIGOT A Novobiocin absorption diffusion and excretion studies a preliminary report, In Antibiotics Annual 1956–1957 New York Medical Encyclopedia Inc 1957 pp 392–395
22 DAVID N A AND DAY W R Use of a new tetracycline novobiocin combination in the treatment of various types of infection AM&CT 5 128 134 1958
23 DAY H J CONRAD F G AND MOORE J E Immunothrombocytopenia induced by novobiocin Am J M Sc 236 475–482 1958
24 DEBONO J E Treatment of undulant fever Lancet I 585–586 1958
25 DUTTA AND COLAH J Postgrad Med I 1958 (Abstr in J A M A 167 96 1958)
6 EDELSON E Clinical trial of novobiocin (cathomycin) in the treatment of primary and secondary syphilis AM&CT 4 725–728 1957
27 EIGELSBACH H T HERRING R D AND HALSTEAD T W In vitro and in vivo activity of novobiocin against Bacterium tularense Bact. Proc p 69 1957
28 FAIRBROTHER R W AND WILLIAMS B L Two new antibiotics Antibacterial activity of novobiocin and vancomycin Lancet I 1177–1178 1956
29 FELIX A J PRIGOT A AND DORSEY G M A clinical evaluation of tetracycline phosphate complex combined with novobiocin in the treatment of soft tissue infections AM&CT 4 821–824 1957
30 FINDLAY C W JR. AND JOHNSON B A Novobiocin antistaphylococcal action in postsurgical diarrheas In Antibiotics Annual 1956–1957 New York Medical Encyclopedia Inc 1957 pp 202–207
31 FINLAND M AND NICHOLS R L Novobiocin Antibiotica et chemotherapia 4 209–392 1957
32 FROST B M., AND VALIANT M E A microbial method for the determination of novobiocin in body fluids Antib & Chemo 6 648–652 1956

bacitracin, they recommended that novobiocin and chloramphenicol the only two that would be used systemically, be reserved for significant staphylococcal infections that could not be controlled by other means Cooper and Keller[19] in a similar study carried out in 1956–1957 with staphylococci of phage pattern 42B/44A/47C/52/80/81 isolated from patients and family contacts found them to be sensitive to the same four antibiotics and resistant to tetracyclines penicillin and streptomycin It would therefore seem advisable that agents like bacitracin and chloramphenicol and at present kanamycin and neomycin be the drugs of choice for use in combination with novobiocin in order to utilize the latter antibiotic to its best advantage The use of some of these agents however, will obviously have to be limited to life threatening cases in view of the toxicity of the second agent notably neomycin

CONCLUSIONS

Novobiocin is an active antibacterial agent with a spectrum that embraces most gram positive bacteria and a selected number of gram negative ones Its major therapeutic value at present is against staphylococcal infections particularly those resistant to other antibiotics in common use namely penicillin streptomycin erythromycin and the tetracyclines Novobiocin may have some value in infections caused by other gram positive organisms and certain gram negative ones notably in some cases of urinary tract infections due to relatively susceptible strains of *Proteus* particularly when other effective antibiotics have failed or cannot be tolerated The therapeutic usefulness of novobiocin is limited on the one hand by the relative frequency with which its use for periods of a week or more gives rise to skin rashes and on the other hand by the tendency of bacteria particularly staphylococci and organisms found in urinary tract infections to become resistant to it in vitro and during treatment Because of the latter effect novobiocin should always be used together with another antibiotic to which the infecting organism is at least moderately sensitive and each should be given in the dosage appropriate for that agent in the particular type of case under treatment

BIBLIOGRAPHY

1 Anon Announcement Antib Med *2* 172 1956
2 Baadj A G Loperfido F J and Prigot A Treatment of soft tissue infections in children with an antibiotic combination tetracycline and novobiocin with meta phosphate AM&CT *5* 664–668 1958
3 Baden W F Staphylococcal and subsequent *Candida albicans* enterocolitis complicating novobiocin therapy Am J Obst & Gynec *74* 47–52 1957
4 Barber M Czillag A and Medway A I Staphylococcal infection resistant to chloramphenicol erythromycin and novobiocin effect of antibiotic combinations on the emergence of resistant strains Brit M J *2* 1377–1380 1958
5 Barbiers A R and Lewis C N A study of *in vitro* and *in vivo* methods for determining antibiotic synergism Bact Proc p 67 1957

59 LEPPER, M H DOWLING H F JACKSON G G SPIES H W AND MELLODY M The effect of the routine use of novobiocin and spiramycin in combination on the antibiotic sensitiveness of hospital staphylococci *In* Antibiotics Annual 1956–1957 New York Medical Encyclopedia Inc 1957 pp 640–647
60 LIMSON B M AND ROMANSKY M J Novobiocin, a new antibiotic Laboratory and clinical evaluation of thirty patients with bacterial pneumonia Antib Med *2* 277–281 1956
61 LIN F K AND CORIELL, L L Novobiocin, a laboratory and clinical evaluation, Antib Med *2* 268–276 1956
62 LIN F K AND CORIELL, L L The effect of combined antibiotics on the in vitro emergence of staphylococci resistant to novobiocin AM&CT *4* 35–39 1957
63 LOWBURY E J L Chemotherapy for *Staphylococcus aureus* Combined use of novobiocin and erythromycin and other methods in the treatment of burns Lancet *2* 305–310 1957
64 LUBASH, G VAN DER MEULEN J BERNTSEN C JR AND TOMPSETT R Novobiocin a laboratory investigation Antib Med *2* 233–240 1956
65 MCCUNE R M., JR DINEEN P A P AND BATTEN J C The effect of antimicrobial drugs on an experimental staphylococcal infection in mice Ann New York Acad Sc *65* 91–102 1956
66 MARTIN R CHABBERT Y AND SUREAU B La novobiocine son activite experimental «in vitro» et «in vivo» son interet dans les affections graves a staphylococques Presse med *64* 1597–1600 1956
67 MARTIN W J HEILMAN F R NICHOLS D R WELLMAN W E AND GERACI J E Streptonivicin (Albamycin) a new antibiotic preliminary report, Proc Staff Meet Mayo Clin *30* 540–551 1955
68 MARTIN W J HEILMAN F R NICHOLS D R WELLMAN W E AND GERACI J E Novobiocin further observations Antib Med *2* 258–267 1956
69 NICHOLS R. L AND FINLAND M Novobiocin a limited bacteriologic and clinical study of its use in forty five patients Antib Med *2* 241–257 1956
70 NOYES H E NAGLE S C JR SANFORD J P AND ROBBINS M L Novobiocin and PA 105 in vitro and in vivo studies on effectiveness against *Micrococcus pyogenes* Antib & Chemo *6* 450–455 1956
71 PEARSON J Z SOMBERG A ROSENTHAL, I LEPPER M H JACKSON G G AND DOWLING H F A clinical and bacteriologic evaluation of novobiocin in 75 patients A M A Arch Int Med *98* 273–283 1956
72 PULASKI, E J AND ISOKANE, R K Novobiocin therapy of pyogenic surgical infections Surg Gynec & Obst *104* 310–318 1957
73 RANTZ L A RANDALL E THUM L AND BARKER, L F The effects of vancomycin oleandomycin and novobiocin on staphylococci in vitro Antib & Chemo *7* 399–409 1957
74 ROBINSON H J AND SILBER R Personal communication to DAVID N A AND BURGNER, P R Antib Med *2* 219–229 1956
75 ROLLAND G SENSI P DE FERRARI, G A MAFFII, G TIMBAL M T AND SILVESTRI L G *Sulla* novobiocina ed alcuni suoi derivati Il Farmaco Ed. Sc *11* 549–561 1956
76 SANFORD J P HATTEN B E AND FORDTRAN J S Effectiveness of novobiocin and cycloserine on *Nocardia asteroides In* Antibiotics Annual 1957–1958 New York Medical Encyclopedia Inc 1958 pp 22–26
77 SENECA H LATTIMER, J K AND JOHNSON A The place of novobiocin in genitourinary tract infections J Urol *79* 882–889 1958
78 SERY T W PAUL S D AND LEOPOLD I H Novobiocin a new antibiotic Ocular penetration and tolerance Arch Ophth *57* 100–109 1957
79 SHIDLOVSKY B A MARMELL, M AND PRIGOT A Novobiocin used alone and in combination with neomycin for bowel sterilization *In* Antibiotics Annual 1956–1957 New York Medical Encyclopedia Inc pp 232–235
80 SHUNK, C H STAMMER C H KACZKA E. A WALTON E SPENCER C F WILSON A N RICHTER, J W HOLLY F W AND FOLKERS K. Novobiocin. II Structure of novobiocin J Am Chem Soc *78* 1770–1771 1956
81 SIMON H J MCCUNE R. M DINEEN P A P., AND ROGERS D E. Studies on novobiocin a new antimicrobial agent Antib Med *2* 205–218 1956
82 SIMON H J AND ROGERS D E. Agranulocytosis associated with novobiocin administration report of a case Ann Int Med *46* 778–784 1957

33 FROST B M VALIANT M E MCCLELLAND L SOLOTOROVSKY M AND CUCKLER A C The antimicrobial activity of cathomycin a new antibiotic *In* Antibiotics Annual 1955–1956 New York Medical Encyclopedia Inc 1956 pp 918–923
34 GARROD L. P AND WATERWORTH P M Behaviour *in vitro* of some new anti staphylococcal antibiotics Brit M J *2* 61–65 1956
35 GARRY M W A clinical evaluation of the parenteral use of novobiocin Am J M Sc *236* 330–335 1958
36 GARSON W AND MCLEOD C P The effect of novobiocin on experimental syphilis *In Antibiotics Annual 1956–1957* New York, *Medical Encyclopedia Inc 1957* pp 1073–1076
37 GAUSE G F Recent studies on albomycin a new antibiotic Brit M J *2* 1177–1179 1955
38 GIUSTI M AND MORI S Novobiocin in the treatment of staphylococcal meningitis Riv clin pediat *61* 177–194 1958
39 GOLDBERG L C Treatment of cutaneous infections with tetracycline novobiocin combination AM&CT *5* 125–127 1958
40 GOST J F Treatment of undulant fever Lancet *1* 191–192 1958
41 GREEN D C BAKER H J EVANS J R PENDERGAST P A AND LINDBERG R B Novobiocin therapy in puerperal mastitis *In* Antibiotics Annual 1957–1958 New York, Medical Encyclopedia Inc 1958 pp 14–21
42 HAAS K B CONNOR N D AND DAVIDSON J L Oral use of a new antibiotic in cats and dogs Vet Med *51* 581–583 1956
43 HERROLD R D Some considerations in the administration of novobiocin and cycloserine J Urol *77* 771–772 1957
44 HINE R B AND BUTLER E E Use of novobiocin for isolation of fungi from the soil Phytopathol *47* 524 1957
45 HINMAN J W CARON E L AND HOEKSEMA H The structure of novobiocin J Am Chem Soc *79* 3789–3800 1957
46 HOEKSEMA H BERGY M E JACKSON W G SHELL J W HINMAN J W FONKEN A E BOYACK G A CARON E L FORD J H DEVRIES W H AND CRUM G F Streptonivicin a new antibiotic II Isolation and characterization Antib & Chemo *6* 143–148 1956
47 HOEKSEMA H CARON E L AND HINMAN J W Novobiocin III The structure of novobiocin J Am Chem Soc *78* 2019–2020 1956
48 HUGHES J COPPRIDGE W M AND ROBERTS L C Chronic urinary infections results of treatment with novobiocin AM&CT *5* 559–561 1958
49 HUGHES J G Apparent sensitization to novobiocin Case report J Pediat *51* 664–666 1957
50 JAMES A P R Clinical evaluation of combination of tetracycline phosphate complex and novobiocin AM&CT *4* 797–799 1957
51 JAWETZ E BERTIE W AND SONNE M *The participation of novobiocin* and vancomycin in combined antibiotic action against staphylococci AM&CT *4* 40–44 1957
52 JOHNSON F T PERRY J J AND SOKOLSKI W T Effect of a novobiocin sulfonamide combination on organisms generally associated with urinary tract infections *In* Antibiotics Annual 1957–1958 New York Medical Encyclopedia Inc 1958 pp 27–30
53 JONES W F JR Quoted in Finland and Nichols [31] p 265
54 JONES W F JR AND FINLAND M Antibiotic combinations antibacterial action of plasma after ingestion of novobiocin or penicillin G or both New England J Med *257* 1268–1274 1957
55 JONES W F JR NICHOLS R. L AND FINLAND M *Antibacterial activity of* streptonivicin and cathomycin two new antibiotics J Lab & Clin Med *47* 783–792 1956
56 KIRBY W M M HUDSON D G AND NOYES W D Clinical and laboratory studies of novobiocin a new antibiotic A M A Arch Int Med *98* 1–7 1956
57 KIRSHBAUM A KRAMER J ARRET B AND WINTERMERE D M *Microbial assays* of novobiocin in pharmaceuticals and biologic fluids Antib & Chemo *6* 504–510 1956
58 LARSON E. J CONNOR, N D SWOAP O F RUNNELLS R A PRESTRUD M C EBLE T E. FREYBURGER W A VELDKAMP W AND TAYLOR, R M Novobiocin a new antibiotic VI Toxicology Antib & Chemo *6* 226–230 1956

Chapter V | Vancomycin

William M M Kirby
Professor of Medicine University of Washington School of Medicine
Seattle Wash

HISTORY AND DEVELOPMENT

Discovery Vancomycin is produced by a previously unidentified organism to which the name *Streptomyces orientalis* n sp has been assigned The first culture was isolated from a soil sample obtained by a missionary in the tropical jungle of Indonesia and two other strains were later isolated from samples of Indian soil [20] All three cultures appear to belong to the same species but differ from all others described in the available literature

Purification and Chemistry McCormick et al[18] and Higgins and co workers[12] have presented methods for isolation and purification of vancomycin The original papers should be consulted for details of adsorption of the active principle on resin and separation of crystalline vancomycin from amorphous material Vancomycin hydrochloride is a white solid very soluble in water moderately soluble in aqueous methanol and insoluble in higher alcohols acetone and ether There appears to be no significant chemical relationship to any other known antibiotic The molecule is very large with a molecular weight of approximately 3300 The best preparations of vancomycin have contained 4 per cent chlorine 10 per cent carbohydrate and 9 per cent aspartic acid Electrophoretic studies have shown that crystalline vancomycin contains 20 per cent or more of a second component the biological activity of which has not been determined Consequently until these components have been separated the ultimate composition and biological activity of vancomycin remain indefinite

83 SMITH C G DIETZ A SOKOLSKI W T AND SAVAGE G M Streptonivicin a new antibiotic I Discovery and biologic studies Antib & Chemo *6* 135-142 *1956*
84 SPITZY K H Ueber die Bestimmung des Verteilungsvolumens der Antibiotika im Koerper am Beispiel von Penicillin und Novobiocin Presented at the First European Symposium on the Biochemistry of Antibiotics in Milan Sept. 9-13 1956
85 STAPLEY E O AND ORMOND R E Similarity of albomycin and grisein Science *125* 587-589 *1957*
86 TALL M G CORIELL L L AND GASKILL H Novobiocin and tetracycline phosphate in the treatment of scarlet fever *In* Antibiotics Annual *1957-1958* New York Medical Encyclopedia Inc *1958* pp 927-932
87 TAYLOR R M MILLER W L AND VANDER BROOK M J Streptonivicin a new antibiotic V Absorption distribution and excretion Antib & Chemo *6* 16?-170 1956
88 TENNENT D M MASON R C KURON G W VALIANT M E AND SOLOTOROVSKY M Binding of novobiocin with plasma proteins Proc Soc Exper Biol & Med *94* 814-815 *1957*
89 THAYER J D PERRY M I FIELD F W AND GARSON W Failure of penicillin chloramphenicol erythromycin and novobiocin to kill phagocytized gonococci in tissue culture *In* Antibiotics Annual 1956-1957 New York Medical Encyclopedia Inc 1957 pp 513-517
90 TUNEVALL G Personal communication Feb 1 1957
91 VAN DER MEULEN J LUBASH G AND TOMPSETT R Treatment of pneumonia with novobiocin AM&CT *5* 26-35 *1958*
92 VERWEY W F MILLER A K AND BARON B J Novobiocin penicillin combinations I The antibacterial interaction between novobiocin and penicillin *In* Antibiotics Annual 1957-1958 New York Medical Encyclopedia Inc *1958* pp 31-37
93 VERWEY W F MILLER A K AND WEST M K A laboratory evaluation of the chemotherapeutic properties of cathomycin *In* Antibiotics Annual *1955-1956* New York Medical Encyclopedia Inc *1956* pp 924-928
94 WALLICK, H HARRIS D A REAGAN M A RUGER M AND WOODRUFF H B Discovery and antimicrobial properties of cathomycin a new antibiotic produced by *Streptomyces spheroides* n sp *In* Antibiotics Annual 1955-1956 New York, Medical Encyclopedia Inc *1956* pp *909-917*
95 WELCH H LEWIS C N PUTNAM L E AND RANDALL W A. A study of the sensitizing potential of novobiocin AM&CT *3* 27-32 1956
96 WILKINS J R GRAY J E NIKITAS C T AND PRETRUD M C The effect of a new antibiotic novobiocin on the course of an experimental *Staphylococcus* infection in mice *In* Antibiotics Annual 1956-1957 New York, Medical Encyclopedia Inc 1957 pp 1063-1072
97 WILKINS J R LEWIS C AND BARBIERS A R Streptonivicin a new antibiotic III In vitro and in vivo evaluation Antib & Chemo *6* 149-156 1956
98 WILLCOX R R Novobiocin in the treatment of acute gonorrhea AM&CT *4* 609-612 1957
99 WRIGHT W W PUTNAM L E AND WELCH H Novobiocin serum concentrations and urinary excretion following oral administration in man Antib Med *2* 311-316 1956
100 *YEGIAN D AND BUDD V Novobiocin activity in vitro and in experimental* tuberculosis Am Rev Tuberc *76* 272-278 1957

TABLE I

Relative in Vitro Activity of Three New Antibiotics Against Recently Isolated Strains of Staph au eus

		Inhibitory concentration μg/ml				
Antibiotic	Total no strains	Greater than 10	10	5	2	1
Kanamycin	54	37	8	7	1	1
Ristocetin	32	0	14	18	0	0
Vancomycin	70	0	0	11	57	2

Other studies showing greater in vitro activity of vancomycin than of ristocetin have been reported by Wise [5] Schneierson et al [4] and Rantz and Jawetz [1]

Bactericidal Action During the initial period of assay development an un usually steep dose response curve was noted with vancomycin suggesting the possibility of bactericidal activity [18] Subsequent studies have confirmed the potent bactericidal action of vancomycin against multiplying staphylococci Zeigler et al [6] studied population changes with plate counts and noted that 2 μg/ml of the antibiotic caused virtual sterilization of a culture containing a relatively large inoculum of staphylococci within 11 hours Concentrations less than 2 μg/ml also caused a marked decrease in colony counts for the first 11 hours after which the culture was able to recover and attain limited multiplication In contrast to antibiotics generally considered to be bacterio static vancomycin was found to cause an immediate killing effect similar to that of penicillin without a lag period. Studies using washed cells showed that vancomycin like other antibiotics exerts its bactericidal action only against multiplying bacteria Geraci and co workers [7, 8] using a serial dilution proce dure observed a total bactericidal effect with 2 5 μg/ml of vancomycin with nine strains of staphylococci and 5 μg with three strains Other workers have also noted that the amount of vancomycin required for a bactericidal effect was the same as or at most one or two tubes higher than the amount needed for bacteriostasis [8, 2] Garrod and Waterworth[5] concluded that vancomycin was the most bactericidal of eight antistaphylococcal antibiotics studied

Wise [5] using a considerably larger inoculum noted that more than 50 μg/ml of vancomycin was needed for total killing with several strains of staphylococci and no bactericidal effect was noted with one culture Kirby et al[15] also observed that a few colonies of staphylococci often grew when tubes containing 100 μg/ml were subcultured after 18 hours It is apparent from these results that with a large inoculum and a relatively short incubation period bactericidal end points obtained with vancomycin are considerably higher than those required for bacteriostasis In comparing the results with

ANTIMICROBIAL ACTIVITY

In Vitro Results Studies by a number of workers have shown that vancomycin has activity against pathogenic bacteria other than staphylococci[8, 10, 11] Since this discussion is concerned mainly with staphylococci results with other bacteria can be simply summarized as follows Sensitive β hemolytic streptococci *Streptococcus faecalis* pneumococci staphylococci *Neisseria gonorrhoeae* nonsensitive *Escherichia coli Alcaligenes Aerobacter Klebsiella Brucella Proteus Pseudomonas Shigella Salmonella Mycobacterium tuberculosis* yeasts and fungi

Pathogenic staphylococci have been found to be almost uniformly sensitive to vancomycin in low concentrations Using a streak plate technique, Geraci et al[7, 8] found that 15 of 112 strains of *Micrococcus pyogenes* were completely inhibited by 1 25 μg /ml 95 by 2 5 μg /ml and 2 by 5 μg /ml Kirby and Divelbiss[14] reported that 51 of 63 strains of *Staphylococcus aureus* were inhibited by 2 μg /ml of vancomycin and 12 required 3 μg Of the 63 strains 52 were resistant to the tetracyclines streptomycin and penicillin and 19 were also resistant to chloramphenicol and erythromycin Schneierson and Amsterdam [3] tested 29 erythromycin resistant strains of staphylococci and noted that 90 per cent of them were sensitive to 2 μg /ml or less of vancomycin Rantz et al[2] found 41 strains of staphylococci sensitive to 5 μg /ml or less and Garrod and Waterworth[5] reported that 54 of 55 strains were sensitive to 1 μg /ml Fairbrother and Williams[4] observed that 540 strains of *Staph aureus* were all sensitive to vancomycin and Ehrenkranz[3] reported inhibition of 21 staphylococcal isolates by 2 μg /ml or less Wise[25] and Jawetz et al[13] also reported a series in which there was uniform inhibition of staphylococci at *concentrations lower than 5 μg /ml Of the hundreds of strains so far studied* only five have shown growth in concentrations greater than 10 μg /ml (Schneierson and Amsterdam[23] three strains Griffith and Peck[10] two strains)

The effect of serum on the bacteriostatic and bactericidal action of vancomycin has been studied [7, 14] Bacteriostatic end points were usually the same in serum as in broth and bactericidal end points were only one or two tubes higher in serum It can be concluded that the action of vancomycin is not greatly affected by the presence of serum

It is also of interest that the activity of vancomycin shows little variability with changes in pH of the test medium Streptomycin was found to be approximately 12 times more active at pH 8 than at pH 6 whereas vancomycin activity was altered less than twofold over the same pH range [6]

Using a large inoculum Kirby et al[15] have recently compared bacteriostatic end points of vancomycin with those obtained with two other new antibiotics ristocetin and kanamycin It is apparent from table I that ristocetin showed less activity than vancomycin and kanamycin was less active than ristocetin

peared so far In a number of patients staphylococci have been observed to retain their susceptibility after two to four weeks of vancomycin therapy[3 7 14 15]

Synergism and Antagonism Jawetz et al[13] observed a few examples of true synergism between vancomycin and either neomycin or bacitracin In these instances two drugs in combination resulted in an early bactericidal rate in excess of that achieved with twice the concentration of either agent alone When vancomycin was combined with chloramphenicol or erythromycin simple additive effects were noted i e the two drugs together accomplished no more than double the concentration of one agent acting alone If vancomycin continues to be effective when used alone its participation in combined antibiotic activity may not prove to be important clinically

Animal Protection Tests Fifty per cent of mice infected intravenously with staphylococci died and the survivors all had abscesses in the kidneys or other organs[7 8] Of mice treated with vancomycin subcutaneously twice daily all who received a daily dosage of 25 mg /Kg survived but total protection against gross lesions required 100 mg /Kg

PHARMACOLOGICAL PROPERTIES

Animal Studies After an intravenous dose of 10 mg /Kg the initial serum concentration of vancomycin in dogs was more than 25 µg /ml[17] The level dropped rapidly during the first 15 minutes and declined rather slowly thereafter giving a biological serum half life of 105 minutes An intramuscular dose of 20 mg /Kg gave a peak level of 10 µg /ml at one hour which persisted for four hours and was still greater than 5 µg /ml at six hours Sixty seven per cent of the intravenous dose was recovered from the urine within 24 hours with the majority being obtained during the first two hours After intramuscular injection about 55 per cent was recovered in the urine mostly during the first six hours Vancomycin was excreted in the bile in small quantities in dogs and was detected in even smaller amounts in cerebrospinal fluid The renal clearance of vancomycin approximated two thirds of the glomerular filtration rate based on the filterable fraction of the plasma vancomycin The antibiotic passed through the placenta from maternal blood to fetal blood and to amniotic fluid in rabbits and from blood to milk in cats in significant amounts High concentrations of vancomycin were found in the kidneys of rats and rabbits and small amounts were present in the spleen and liver six hours after intravenous doses[16]

Absorption and Excretion in Man Serum concentrations of vancomycin after single intravenous doses administered over a 20 to 30 minute period in adult men are depicted in figure 1[14] The figures on the chart represent the averages of levels obtained in 2 patients for 0 5 Gm 4 patients for 1 Gm

various antibiotics it is obviously important to standardize the conditions under which the tests are performed

A few studies are available indicating that vancomycin is a more potent bactericidal antibiotic than ristocetin For example Wise[25] found that vancomycin was bactericidal against all but 1 of 13 strains of staphylococci, whereas ristocetin was lacking in bactericidal action against 12 of 13 cultures Schneierson et al [4] noted that ristocetin failed to prove lethal with 60 of 101 strains of *Staph aureus* and concluded that the action of ristocetin against this microorganism is with rare exceptions primarily bacteriostatic rather than bactericidal Rantz and Jawetz [1] in studying 42 strains of *Staph aureus* found that bactericidal concentrations of ristocetin were threefold to more than tenfold greater than the 24 hour inhibitory concentrations With vancomycin [2] using the same technique bactericidal and inhibitory concentrations were the same for 37 of 41 strains and in the other four the bactericidal concentration was one tube greater It is the opinion of the author that further studies of the relative bactericidal action of antistaphylococcal antibiotics are needed with careful attention devoted to variables that might influence the results An excellent approach to this problem has recently been described by Grundy et al [11]

Resistance A number of workers have observed that resistance of staphylococci to vancomycin develops very slowly in vitro Ziegler et al [8] observed a 131 056 fold increase in the concentration of penicillin tolerated by *Staph aureus* 209P after 25 exposures while the same bacterial culture was able to tolerate only a four to eightfold higher concentration of vancomycin after the same number of exposures Other staphylococci exhibited an almost identical pattern of resistance to vancomycin Using a serial subculture technique Griffith and Peck[10] found that resistance to vancomycin did not develop in 10 strains of *Staph aureus* after 25 subcultures in media containing various concentrations of the antibiotic Garrod and Waterworth [5] on the basis of their studies commented that resistance to vancomycin of such a degree as to preclude therapeutic effect apparently cannot develop in staphylococci at all A relatively small degree of resistance was also reported by Geraci et al[7, 8] after 28 daily subcultures Resistance was acquired gradually and in small steps and both strains made resistant became rather dysgonic growing more slowly in broth and forming smaller colonies on agar than did the original strains Using somewhat different techniques Rantz et al [2] and Jawetz et al[13] also observed that staphylococci did not develop resistance to vancomycin in vitro In contrast Jawetz et al reported a 10 fold to more than 30 fold increase in resistance after a single exposure to novobiocin

These in vitro observations suggest that the development of vancomycin resistant staphylococci may be an infrequent occurrence in patients During rather limited trials over a three year period resistant strains have not ap

No vancomycin could be detected in the blood after oral administration in normal subjects but a trace was found in the blood of 1 patient who was treated for staphylococcal ileocolitis [7] Urine specimens collected after oral administration indicated that *small quantities were absorbed* since assayable amounts appeared in the urine Urinary concentrations were usually less than 3 μg/ml but for unexplained reasons values of 110 and 170 μg/ml of urine were obtained in a few persons [7] Very large quantities of vancomycin were excreted in the stool after oral administration Intramuscular injections of vancomycin have been associated with mild to moderate pain [10] and administration has therefore been limited chiefly to the intravenous route

Diffusion into Body Fluids and Tissues in Man Vancomycin has been found to diffuse readily into pleural ascitic and synovial fluids with concentrations being considerably higher after multiple than after single doses [7] Data in regard to pericardial fluid are less clear cut since some of the specimens were contaminated with blood Small quantities of vancomycin have been recovered from bile indicating that the drug is not concentrated there The antibiotic does not pass into the spinal fluid through the normal meninges even after multiple doses but vancomycin has been found to penetrate into the spinal fluid in some instances when the meninges are inflamed as a result of infection [9 14]

TOXICITY AND SIDE EFFECTS

Animal Studies Acute studies showed that vancomycin has a low order of toxicity in mice rats and guinea pigs [1] In monkeys and dogs intravenous dosage of 25 to 50 mg/Kg daily for three months or longer produced no signs of toxicity Hematological studies revealed no definite changes in the peripheral blood and terminal bone marrow studies showed no abnormalities There was no alteration in blood urea nitrogen determinations There was no evidence of eighth nerve damage in cats receiving 50 mg/Kg intramuscularly for eight weeks Previous studies had shown nystagmus and loss of righting reflexes with similar doses of streptomycin for only four weeks Vancomycin had little or no effect on the blood pressure respiration electrocardiogram intestinal motility urinary flow or isolated gut of experimental animals [1]

Observations in Man With the early lots of vancomycin pain at the site of intravenous injection and chemical thrombophlebitis occurred frequently Purification of the antibiotic has greatly ameliorated this problem With the relatively pure antibiotic powder available during the past year phlebitis has occurred in some patients but this has usually caused little difficulty In general there has been little more irritation of veins than is present when glucose solutions are administered separately In a number of patients vancomycin was administered through femoral or caval catheters with no apparent

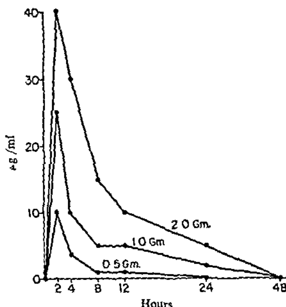


FIG 1 Serum concentrations of vancomycin after single intravenous doses administered over a 20 to 30 minute period

and 6 patients for 2 Gm Similar results were obtained in the study of Geraci et al although levels during the first hour were higher since the antibiotic was administered over a four minute period In the studies of both Kirby and Divelbiss[14] and Geraci et al[7] there was some tendency toward a cumulative action when doses were given at 6 to 12 hour intervals Geraci et al obtained an average value of 8 4 μg /ml three hours after multiple 0 5 Gm doses at six hour intervals From the standpoint of ease of administration and the maintenance of effective levels Kirby and Divelbiss felt that 1 Gm every 12 hours appeared to be the most desirable regimen

In patients with impaired renal function much higher serum concentrations were obtained[14] One patient who maintained a blood urea nitrogen of 40 mg /100 ml throughout the course of therapy had 24 hour blood levels of 20 to 33 μg /ml for a period of eight days and the concentration was still 5 μg /ml nine days after discontinuing therapy Another who received 2 Gm every 12 hours and whose blood urea nitrogen was between 40 and 50 per cent was found to have 12 hour levels of 100 μg / ml on three occasions

Vancomycin is excreted chiefly through the kidneys Kirby and Divelbiss[14] recovered more than 80 per cent of the dose administered within a 24 hour period and high urinary concentrations were also reported by Geraci et al[8] and by Griffith[9] Excretion of 30 to 40 per cent of an intravenous dose in 24 hours was reported by Griffith Because of large errors in the assay method it is not possible to reconcile these somewhat variable results in man or to compare them with those obtained by Lee et al in dogs[17]

of vancomycin hydrochloride in 10 ml rubber stoppered ampoules * At the time of use 10 ml of water for injection U S P is added to the ampoule of dry sterile vancomycin powder Administration is only by the intravenous route and can be accomplished in any of the following ways (1) Direct injection Ten ml (500 mg vancomycin) can be injected directly into a large arm vein using a 10 ml syringe This injection should be given slowly over at least a four minute period This can be repeated at six- to eight hour intervals so that the total daily dosage will be 1 5 to 2 0 Gm (phlebitis appears to be more frequent with this method) (2) Rapid infusion Ten to 20 ml (0 5 to 1 Gm) can be added to 100 to 200 ml of normal saline or 5 per cent glucose This intravenous infusion can be given rapidly over a period of 20 to 30 minutes every 12 hours so that the patient will receive 1 to 2 Gm /day Smaller amounts can be given every six to eight hours but this probably offers no advantages (3) Continuous injection Two to 4 ampoules (1 to 2 Gm) can be added to a 1000 or 2000 ml bottle of normal saline or 5 per cent glucose This can be administered slowly by drip over a 24 hour period so that the patient receives 1 to 2 Gm /day (4) If the patient is receiving continuous intravenous fluids containing material with which vancomycin may not be compatible it is possible to dilute the vancomycin as in method 2 and switch bottles

Method 2 is the one preferred by the author and the usual daily dosage for adults is 1 Gm every 12 hours Three or four Gm daily may be given initially if the patient has an overwhelming infection and the blood urea nitrogen is normal After the infection has been brought under control (ordinarily in five to seven days) a single dose of 1 Gm can be administered daily Dosages larger than 2 Gm daily are not often indicated The antibiotic may be administered at six or eight hour intervals but this probably offers no advantages and is considerably more difficult when a new intravenous infusion is started for each dose For infections in children vancomycin may be used in a dosage of 20 mg /lb of body weight daily Blood and urine concentrations that can be anticipated with the dosages referred to have been presented in the section on pharmacological properties and will not be repeated here

USE IN STAPHYLOCOCCAL DISEASE

Vancomycin did not become available commercially until late 1958 and it has been used clinically in a relatively small number of patients In addition to clinical trials reported in the medical literature the author has had access to unpublished case reports from dozens of investigators which were collected by the Eli Lilly & Company and submitted to the Federal Food and Drug Administration as part of the application for approval Although some of the

* The trade name of Eli Lilly & Co for vancomycin is Vancocin

deleterious effects Phlebitis can be minimized by using relatively dilute solu tions and by alternating the sites of injection Rapid intravenous injection has also caused a feeling of warmth and generalized tingling in some patients but does not occur when the dose is given over a period of 20 to 30 minutes

As is true with some other compounds of high molecular weight, reactions characterized by chills fever urticarial eruptions or macular rashes have occurred during or after the administration of vancomycin in some patients These reactions were quite common with the early lots and are still encoun tered but have occurred less frequently during the past year When they do occur the drug should be discontinued at once the symptoms seem to be alleviated by administration of antihistamines In some patients we have been able to continue vancomycin by administering antihistamines with the intra venous infusion for several days and there have been no further reactions when the antihistamines were then stopped In other patients vancomycin was tolerated several months later without reactions In 2 patients a rash occurred with vancomycin and ristocetin was then used for therapy without side effects We have similarly noted patients who developed a rash with ristocetin but tolerated vancomycin without difficulty Three patients with fever rash and ringing in the ears had previously received prolonged anti biotic therapy for osteomyelitis suggesting the possibility of cross sensitization with other antibiotics such as streptomycin [15]

Slight renal irritation was noted in a few instances with early impure lots of vancomycin [14] but signs of nephrotoxicity have been completely lacking during the past year [15] In no instance has there been an abnormality of the urinary sediment and in a number of cases there was a decline in the blood urea nitrogen while the patient was on therapy The manifestations of renal irritation previously noted appear to have been eliminated by the preparations of vancomycin now available There has also been no evidence of hematologi cal or hepatic toxicity reported so far

Deafness has been described in association with very high vancomycin serum concentrations in a few patients [6, 9] Decreased auditory acuity has oc curred with blood levels in excess of 90 μg /ml which is 5 to 10 times greater than the necessary therapeutic concentration Because of these obser vations vancomycin should be used cautiously in patients with reduced renal function with determinations of blood urea nitrogen and auditory acuity every two to three days The dosage of vancomycin should be lowered in proportion to the degree of renal insufficiency and blood levels of vancomycin should be determined if feasible

DOSAGE FORMS AND METHODS OF ADMINISTRATION

Vancomycin is available so far in only one dosage form namely as 0 5 Gm

there have also been disappointing failures At autopsy abscesses have invariably been present in a number of organs other than the lungs

Ehrenkranz[3] has recently reported good results in several cases of staphylococcal pneumonia after other antibiotics had failed The detailed case reports included in his paper would be particularly helpful to those confronted with similar problems

The role of vancomycin therapy in treating staphylococcal empyema has not been clearly delineated As noted in the section on pharmacological properties the antibiotic diffuses readily into pleural fluid In the series reported by Ehrenkranz a 13 year old boy with staphylococcal empyema was treated successfully with vancomycin after catheter drainage and therapy with other antibiotics had apparently failed On the other hand Geraci et al[7] discontinued vancomycin after four doses because no antibiotic could be demonstrated in an empyema pocket It is apparent that more experience is needed before any conclusions can be drawn One of the most important features of the treatment of staphylococcal empyema will undoubtedly continue to be surgical drainage[19]

Staphylococcal Septicemia and Endocarditis Despite difficulties in clinical evaluation and the relatively small number of cases so far treated promising results have been obtained in patients with blood stream infections caused by antibiotic resistant staphylococci In a number of instances there has been a dramatic response to vancomycin therapy after other antibiotics had failed In patients with overwhelming septicemias and in those with deep seated abscesses throughout the tissues there have also been a number of failures

Geraci et al[6] obtained unsatisfactory results with multiple antibiotic therapy in acute staphylococcal endocarditis over a period of several years Five of 23 patients were cured with penicillin streptomycin therapy but these were all cases of the chronic or subacute type No patients with acute staphylococcal endocarditis were cured prior to the advent of vancomycin in 1956 Subsequently 4 of 6 patients were cured by vancomycin and a fifth died of congestive failure two weeks after therapy was terminated with the infection under control blood cultures negative and the lesions healing The sixth patient who also died of intractable congestive failure had a severe and fulminating infection which was not controlled by vancomycin therapy The 4 patients for whom treatment was successful received vancomycin for 28 20 28 and 18 days respectively The killing effect shown by serum bactericidal tests in all cases was so good that the authors suggested that short term (two weeks) vancomycin therapy might be practical and curative This regimen with a single antibiotic is in marked contrast to the four to six weeks of therapy previously given with massive dosages of penicillin combined with streptomycin probenecid and either erythromycin or bacitracin Administration of

conclusions must be considered rather tentative the total clinical experience has been sufficient to make a preliminary evaluation

Staphylococcal Infections of Skin and Soft Tissues Results in soft tissue infections have been uniformly good which is not surprising in view of the potent bactericidal action of vancomycin A prompt response to therapy has been noted in patients with cellulitis recurrent furunculosis and large carbuncles[7 10 14 15] Surgical drainage is often an important adjunct to therapy Because of difficulties in administration vancomycin should be reserved for cases in which there has been a failure to respond to other antibiotics to those caused by antibiotic resistant staphylococci and to instances in which the lesions are potentially life threatening as in deep carbuncles and in cellulitis about the face

A good response to vancomycin has been reported in a number of patients with deep postoperative wound infections[7 9 14] In such instances vancomycin may be considered the drug of choice in view of the likelihood that the etiological organisms are antibiotic resistant staphylococci and the tendency for these deep seated infections is to spread to other organs through the blood stream Good results have also been reported in patients with postoperative staphylococcal enterocolitis[7 9] In some of these cases vancomycin has been given by the oral route alone

Staphylococcal Pneumonia and Empyema Primary staphylococcal pneumonia is relatively rare In the majority of instances pneumonia caused by this organism results from aspiration either postoperatively or in debilitated patients who fall prey to this ubiquitous organism while they are receiving treatment in the hospital for other diseases The author and his associates[15] recently reported the results of vancomycin therapy in 8 such patients at the King County Hospital 2 of whom had blood cultures positive for staphylococci Defervescence was rather slow in some instances but a good response was obtained in all 8 cases and the duration of therapy varied from 7 to 14 days Despite the fact that the diagnosis was made early multiple lung abscesses formed in several of the cases and in all instances these gradually cleared without the necessity of surgical drainage or resection Failure to respond to therapy has been observed in a number of patients with overwhelming staphylococcal pneumonia These patients were virtually moribund when the diagnosis was made and death occurred after only a few doses of vancomycin had been given

Staphylococcal pneumonia also occurs by hematogenous spread from a focus elsewhere in the body for example osteomyelitis or a deep wound infection Multiple bilateral lung abscesses frequently develop and prognosis is dependent on the severity of the infection the presence of endocarditis and of abscesses in other tissues and the stage of the illness at which vancomycin therapy is instituted The author has observed apparently dramatic cures and

he concluded that vancomycin has an important place in the treatment of severe staphylococcal infections

Unpublished reports by clinical investigators throughout the country deserve brief comment Cures were obtained in 6 patients with staphylococcal septicemia by one investigator and there were also several failures It was noted that blood cultures remained positive for three or four days after vancomycin was started in some patients who were treated successfully This investigator also observed that blood cultures sometimes showed no growth for three or four days after which the broth became cloudy and staphylococci were obtained on subculture Several other cases were reported in which vancomycin brought about an apparent cure after a failure to respond to other antistaphylococcal antibiotics including bacitracin ristocetin neomycin erythromycin and novobiocin

Osteomyelitis Although the number of cases so far treated is small the reports suggest that staphylococcal osteomyelitis and septic arthritis respond to vancomycin in a manner similar to response to penicillin when the infecting organisms are susceptible to that antibiotic In brief acute osteomyelitis is often cured by vancomycin therapy alone whereas in chronic cases there is marked improvement with a decrease in toxicity and closing of draining sinuses but relapses usually occur unless antibiotic therapy is accompanied by removal of necrotic tissue and devitalized bone

Ehrenkranz[3] described a 51 year old man with osteomyelitis and septic arthritis of the right knee with persistent pain and drainage after four months of antibiotic therapy Remarkable improvement occurred with a two week course of vancomycin Cultures of the knee became negative for staphylococci the excess synovial fluid disappeared and the draining and pain subsided A 75 year old man developed staphylococcal arthritis of the knee after a fractured patella He failed to respond to other antibiotics and blood cultures became positive for staphylococci The patient then received a 15 day course of vancomycin therapy and had progressive improvement with subsidence of both local and general symptoms and healing of the knee The third case reported by Ehrenkranz was a 13 year old white boy with osteomyelitis of the right humerus and femur which cleared after a two week course of vancomycin therapy In all 3 cases there seemed to be a definite response to the bactericidal action of vancomycin after antibiotics with a primarily bacteriostatic action had failed to eradicate the infection

Geraci et al[7] also obtained good results in 2 patients with osteomyelitis who received vancomycin therapy in conjunction with surgery Kirby et al[14, 15] treated 4 patients with chronic osteomyelitis with 1 Gm of vancomycin daily for three or four weeks In all cases signs of inflammation subsided and there was a cessation of drainage from sinus tracts In all instances however a relapse occurred within a few weeks to several months later demonstrating

all these agents in high dosage for this long a period was obviously cumber some highly expensive and time consuming

Kirby et al[1] recently reported favorable clinical results in 17 patients with staphylococcal septicemia This is of considerable importance in view of the high mortality rate usually associated with this disease Thirteen of the 17 patients were cured of the infection Two patients died at a later date 1 of metastatic cancer and the other of pyelonephritis secondary to prostatic dis ease At autopsy the latter patient showed evidence of healed staphylococcal endocarditis Of the 4 patients who died during or shortly after therapy the infection seemed to be favorably influenced in 3 One died of a massive gastro intestinal hemorrhage on the sixth day of therapy although her temperature was declining Another 88 years old with a severe wound infection of the hip died of heart failure on the eighth day of therapy although the infection seemed to have responded and she was afebrile A 71 year old woman with fever and positive blood cultures after surgery for cancer of the colon re sponded well to vancomycin and was sent to a nursing home afebrile with negative blood cultures after two weeks of therapy Fever returned two weeks later and the patient died with positive blood cultures and a relapse of staphy lococcal endocarditis Although she was classified as a poor result the initial response to therapy was good in this patient and she might have recovered if treatment had been continued for four to six weeks The fourth patient who was considered a failure had severe third degree burns of the entire body with anuria and hypogammaglobulinemia Only 3 of the 17 patients with staphylococcal septicemia received vancomycin for more than 16 days sug gesting that short term vancomycin therapy may be feasible in some cases as suggested by Geraci et al[6] Of the 13 patients with staphylococcal septicemia who were cured there were a number who responded after other antibiotics had failed and in some the administration of vancomycin was associated with a dramatic drop in temperature and improvement in clinical condition In other instances the temperature declined more slowly but blood cultures became negative and clinical improvement was evident within a few days In 3 cases the blood cultures remained positive for two to four days after van comycin was started although colony counts were markedly decreased on the pour plates

Ehrenkranz[3] treated 10 patients with severe staphylococcal infections with vancomycin after they had failed to respond to at least five days of therapy with other antibiotics Seven of the 10 patients were treated successfully and the 3 who died all had serious underlying medical diseases or metabolic dis orders Four of the 10 had positive blood cultures for staphylococci 2 of these were cured and 2 died Ehrenkranz was impressed with the bactericidal effect of vancomycin at clinically attainable concentrations and the absence of development of vancomycin resistant staphylococci during therapy and

6 GERACI J E HEILMAN F R NICHOLS D R AND WELLMAN W E Antibiotic therapy of bacterial endocarditis VII Vancomycin for acute micrococcal endocarditis preliminary report Proc Staff Meet Mayo Clin *33* 172 1958
7 GERACI J E HEILMAN F R NICHOLS D R WELLMAN W E AND ROSS G T Some laboratory and clinical experiences with a new antibiotic vancomycin Proc Staff Meet Mayo Clin *31* 564–58? 1956
8 GERACI J E HEILMAN F R NICHOLS D R WELLMAN W E AND ROSS G T Some laboratory and clinical experiences with a new antibiotic vancomycin *In* Antibiotics Annual 1956–1957 New York, Medical Encyclopedia Inc 1957 pp 90–106
9 GRIFFITH R. S Personal communication
10 GRIFFITH R S AND PECK F B JR Vancomycin a new antibiotic III Preliminary clinical and laboratory studies *In* Antibiotics Annual 1955–1956 New York Medical Encyclopedia Inc 1956 pp 619–622
11 GRUNDY W E ALFORD E F AND SYLVESTER J C Antibiotic bactericidal studies I Effect of methods on apparent bactericidal concentrations *In* Antibiotics Annual 1958–1959 New York, Medical Encyclopedia Inc 1959 pp 847–854
12 HIGGINS H M HARRISON W H WILD G M BUNGAY H R AND MCCORMICK, M H Vancomycin a new antibiotic VI Purification and properties of vancomycin *In* Antibiotics Annual 1957–1958 New York Medical Encyclopedia Inc 1958 pp 906–914
13 JAWETZ, E BERTIE W AND SONNE M The participation of novobiocin and vancomycin in combined antibiotic action against staphylococci AM&CT *4* 40–44 1957
14 KIRBY W M M AND DIVELBISS C L Vancomycin clinical and laboratory studies *In* Antibiotics Annual 1956–1957 New York, Medical Encyclopedia Inc 1957 pp 107–117
15 KIRBY W M M PERRY D M AND LANE J L Present status of vancomycin therapy of staphylococcal and streptococcal infections *In* Antibiotics Annual 1958–1959 New York Medical Encyclopedia Inc 1959 pp 580–586
16 LEE C-C ANDERSON R C AND CHEN K K Tissue distribution of erythromycin in rats Antib & Chemo *3* 920–924 1953
17 LEE C-C ANDERSON R C AND CHEN K K Vancomycin a new antibiotic V Distribution excretion and renal clearance *In* Antibiotics Annual 1956–1957 New York Medical Encyclopedia Inc 1957 pp 82–89
18 MCCORMICK, M H STARK, W M PITTENGER G E PITTENGER R C AND MCGUIRE J M Vancomycin a new antibiotic I Chemical and biologic properties *In* Antibiotics Annual 1955–1956 New York, Medical Encyclopedia Inc 1956 pp 606–611
19 MAGOVERN G J AND BLADES B Staphylococcic empyema, J A M A *168* 365–369 1958
20 PITTENGER R C AND BRIGHAM R B *Streptomyces orientalis* n sp the source of vancomycin Antib & Chemo *6* 642–647 1956
21 RANTZ L A AND JAWETZ E Failure of ristocetin therapy in three cases of staphylococcal sepsis with bacteremia New England J Med *259* 963–966 1958
22 RANTZ, L A RANDALL, E. THUM L AND BARKER L F The effects of vancomycin oleandomycin and novobiocin on staphylococci in vitro Antib & Chemo *7* 399–409 1957
23 SCHNEIERSON S S AND AMSTERDAM D In vitro sensitivity of erythromycin resistant strains of staphylococci and enterococci to vancomycin and novobiocin Antib & Chemo *7* 251–254 1957
24 SCHNEIERSON S S AMSTERDAM D AND BRYER M S Bacterial sensitivity to ristocetin Antib & Chemo *8* 204–207 1958
25 WISE R I Principles of management of staphylococcic infections J A M A *166* 1178–1182 1958
26 ZIEGLER, D W WOLFE R N AND MCGUIRE J M Vancomycin a new antibiotic II *In vitro antibacterial studies In* Antibiotics Annual *1955–1956* New York, Medical Encyclopedia Inc 1956 pp 612–618

the difficulties in bringing about a permanent cure in osteomyelitis unless definitive surgery can be performed in conjunction with antibiotic therapy The author has recently treated a patient with acute staphylococcal arthritis of the right knee successfully with two weeks of vancomycin intravenously together with repeated aspirations of pus from the joint On one occasion the joint fluid was found to contain 10 µg/ml of vancomycin Another recent patient with staphylococcal arthritis of the right shoulder joint had relapsed twice after therapy with other antibiotics and catheter drainage He became afebrile on vancomycin therapy but again relapsed when it was discontinued *and he is being re treated with vancomycin in addition to open drainage* In septic arthritis as in osteomyelitis it is obviously important to start vancomycin therapy early if surgery is to be avoided A third patient seen recently was a young woman who had severe pain in the left hip and negative roentgenograms of the bones but blood cultures were positive for staphylococci She received 2 Gm of vancomycin daily for two weeks after which she remained afebrile and blood cultures were negative Subsequent films showed the typical roentgenographic changes of acute osteomyelitis and she has shown steady improvement with appropriate orthopedic management

SUMMARY

Vancomycin is a potent bactericidal antibiotic that has given promising therapeutic results in a variety of staphylococcal infections Because of difficulties in administration it should be used chiefly for severe infections unlikely to respond to other antibiotics High serum concentrations are readily obtained and vancomycin resistant staphylococci have so far not been encountered Side effects consisting of chills fever and rashes have occurred in some patients The antibiotic should be given cautiously in the presence of renal insufficiency since excessive serum concentrations of vancomycin have caused deafness in a few patients

BIBLIOGRAPHY

1 ANDERSON R C WORTH H M HARRIS P N AND CHEN K K Vancomycin a new antibiotic IV Pharmacologic and toxicologic studies *In* Antibiotics Annual 1956–1957 New York, Medical Encyclopedia Inc 1957 pp 75–81

2 BREED R S MURRAY E G D AND HITCHENS A P Bergey s Manual of Determinative Bacteriology ed 6 Baltimore Williams & Wilkins Co 1948

3 EHRENKRANZ, N J The clinical evaluation of vancomycin in treatment of multi antibiotic refractory staphylococcal infections *In* Antibiotics Annual 1958–1959 New York Medical Encyclopedia Inc 1959 pp 587–594

4 FAIRBROTHER R W AND WILLIAMS B L Two new antibiotics Antibacterial activity of novobiocin and vancomycin Lancet *2* 1177 1956

5 GARROD L P AND WATERWORTH P M Behaviour in vitro of some new anti staphylococcal antibiotics Brit M J *2* 61 1956

CHEMISTRY

Two closely related substances ristocetins A and B have been obtained in crystalline form from the fermentation broth produced by this actinomycete They are amphoteric substances with molecular weights in the range of 2500 to 4000 [3] and contain amino phenolic and sugar groups in the molecule They are soluble in acid solution less soluble at a neutral *p*H range and insoluble in organic solvents Both compounds have excellent stability in acid solutions but are readily inactivated above *p*H 7 0 They have been isolated as the free bases and crystallized as the sulfates

No clear cut differentiation of the two ristocetins can be made by infrared or ultraviolet absorption spectra anthrone or reducing sugar determinations optical rotation elemental analyses or other chemical tests Separation can be accomplished however by filter paper electrophoresis and paper or carbon column chromatography By the use of broth dilution assays on three strains of *Streptococcus* ristocetin B was found to be three to four times as active as ristocetin A which has an arbitrarily assigned potency of 1000 units/mg [1 23]

Ristocetin is produced by submerged fermentation in a variety of media Media in which soybean meal and glucose are the chief constituents give yields of about 500 µg/ml after three to four days growth The antibiotic is recovered by a carbon adsorption process

STABILITY

Grundy et al[13] noted that the activity of ristocetin is relatively unaffected by blood or serum Six organisms including two staphylococci an enterococcus a hemolytic *Streptococcus* and a strain of *Diplococcus pneumoniae* were tested against the antibiotic by the tube dilution method Identical end points were recorded with the basal medium and media containing either 10 per cent rabbit blood or 20 per cent horse serum

These workers also found that the *p*H of test media does not significantly alter the activity of the antibiotic between *p*H 5 0 and 7 5 At *p*H 7 5 or higher the antibiotic is unstable at 37 C

Studies in our own laboratory indicate that body fluids containing ristocetin may be stored at 10 C for at least five days without deterioration

ASSAY METHODS

Grundy et al[13] have assayed ristocetin by the paper disc plate method of assay a modification of the streptomycin method of Loo et al [19] *Bacillus subtilis* ATCC 10707 is used as a test organism and provides clear sharp zones of inhibition They have also employed a tube dilution procedure using a saphrophytic strain of *Corynebacterium* which will detect 1 25 µg/ml

Chapter VI | Ristocetin

Monroe J Romansky
Professor of Medicine George Washington University School of Medicine
Chief George Washington University Medical Division
District of Columbia General Hospital and
Ray A Olsson
Senior Resident in Medicine George Washington Medical Division
District of Columbia General Hospital Washington D C

HISTORY AND DEVELOPMENT

Although the current period has seen tremendous advances in chemotherapy difficult problems in infectious disease are still present This is particularly so of infections due to the *Staphylococcus* One of the most effective of the newer antibiotics in combatting this type of infection is ristocetin * first isolated by Grundy et al[13] from cultures of *Nocardia lurida*

The latter is an actinomycete that was isolated from a soil sample collected in the Garden of the Gods Colorado Springs Colorado by conventional dilution techniques This new species does not have the characteristics of the previous members of the genus No other actinomycete that produces ristocetin has been found

* The trade name of Abbott Laboratories for ristocetin is Spontin

TABLE I (*Continued*)

Antimicrobial Spectrum of Ristocetin

Culture	Minimum inhibitory concentration µg/ml
Streptococcus pyogenes ATCC 7796	1
Streptococcus uberis ATCC 9927	1
Trichomonas vaginalis C	>50
Trichomonas foetus O	>50
Trichophyton mentagrophytes ATCC 9533	>25
Trichophyton tonsurans ATCC 10217	>25

Resistant to one or more of the commercially available antibiotics
Reprinted with permission from Grundy et al [3]

A turbidimetric method of assay has been described by Eisenberg and Kirschbaum[6] utilizing *Staphylococcus aureus* ATCC 6538p as the test organism

Our technique for assay of ristocetin levels is a modification of the tube dilution method of Rammelkamp[24] By this method 0 625 to 1 25 µg/ml can be detected

ANTIMICROBIAL ACTIVITY

In Vitro Studies Ristocetin is generally specific against gram positive bacteria and mycobacteria A summary of early in vitro tests[13] is presented in table I It is not active against gram negative bacteria including *Hemophilus influenzae Neisseria meningitidis* and *Neisseria catarrhalis* Yeasts filamentous fungi and a few protozoa that were tested were not sensitive

Additional in vitro sensitivity studies were carried out in our laboratory[8] using 235 strains of various microorganisms isolated from hospital patients The results of these studies are shown in table II We have also found ristocetin effective against *Neisseria gonorrhoeae* Studies by Schneierson et al[9] revealed the same pattern of in vitro response based on the determination of minimum inhibitory concentration

Cultures of *Staph aureus* that are resistant to one or several of the commercially available antibiotics including penicillin streptomycin chloramphenicol the tetracyclines erythromycin polymyxin B novobiocin and oleandomycin are responsive to ristocetin Cross resistance between ristocetin and these antibiotics apparently does not occur[13, 8, 9] In our laboratory we have not observed cross resistance between ristocetin and vancomycin or kanamycin

TABLE I

Antimicrobial Spectrum of Ristocetin

Culture	Minimum inhibitory concentration, µg/ml
Actinomyces bovis ATCC 10049	2
Aerobacter aerogenes ATCC 129	>100
Aspergillus niger ATCC 6277	>25
Bacillus cereus ATCC 7064	12.5
Bacillus subtilis ATCC 10707	0.5
Candida albicans ATCC 10231	>25
Chaetomium globosum ATCC 6205	>25
Clostridium perfringens ATCC 10543	0.25
Clostridium sporogenes ATCC 10000	2.0
Clostridium tetani ATCC 9441	0.5
Corynebacterium pseudodiphtheriticum ATCC 6981	0.125
Corynebacterium pyogenes ATCC 8164	2
Diplococcus pneumoniae ATCC 6301	2
Diplococcus pneumoniae ATCC 6303	2
Endamoeba histolytica NRS	>50
Escherichia coli ATCC 6880	>100
Hemophilus influenzae ATCC 9333	>50
Klebsiella pneumoniae ATCC 10031	>100
Lactobacillus casei ATCC 7469	>100
Lactobacillus plantarium ATCC 8014	>100
Leuconostoc mesenteroides ATCC 8042	>100
Staphylococcus aureus ATCC 6538P	4
Staphylococcus aureus Lilly 25592	8
Staphylococcus aureus MIB*	8
Staphylococcus aureus MIK*	8
Staphylococcus aureus 1251*	8
Staphylococcus aureus 1244C*	8
Staphylococcus aureus MIH 5*	8
Myrothecium verrucaria ATCC 9095	>25
Mycobacterium smegmatis ATCC 10143	0.5
Mycobacterium species ATCC 607	0.5
Mycobacterium tuberculosis H_{37}Rv	2.0
Neisseria catarrhalis ATCC 7900	>50
Neisseria meningitidis ATCC 6253	50
Nocardia asteroides ATCC 9970	>50
Proteus vulgaris ATCC 6897	>100
Pseudomonas aeruginosa ATCC 10145	>100
Rhodotorula rubra NRRL Y 1592	>100
Saccharomyces pastorianus ATCC 2366	>100
Saccharomyces cerevisiae X44	>100
Salmonella paratyphi ATCC 9150	>100
Salmonella schottmulleri ATCC 9149	>100
Salmonella typhosa ATCC 9992	>100
Sarcina lutea ATCC 9341	1
Serratia marcescens ATCC 64	>100
Shigella dysenteriae ATCC 9583	>100
Streptococcus agalactiae ATCC 9925	2
Streptococcus dysgalactiae ATCC 9926	1
Streptococcus faecalis ATCC 10541	4
Streptococcus pyogenes ATCC 8668	0.5
Streptococcus pyogenes ATCC 9342	0.5

Table I Continued on Page 141

TABLE II (*Continued*)

Ristocetin Minimum Inhibitory Concentrations for 235 Microorganisms*
(Tube Dilution Method)

*Ristocetin * in Vitro Sensitivity Tests with 15 Strains of Gram negative Microorganisms*

Microorganism	No of strains	µg /ml
Friedlander s bacillus	6	>50
Proteus	2	>50
Colon intermediate	1	>50
Salmonella paratyphi	1	>50
Escherichia coli	1	>50
Ps aeruginosa	1	>50
H influen ae	3	>50

* Ristocetin lot no E 5330 (purity 500 µg /mg)

Mode of Action Early studies by Grundy et al[11] of the antimicrobial activity of ristocetin indicated that bactericidal concentrations only slightly exceeded bacteriostatic levels This is illustrated in table III which summarizes their study of *Staphylococcus albus* 3519 an organism isolated from a patient with bacterial endocarditis Their twofold serial dilution studies revealed only a one tube difference between the minimum inhibitory concentration at 24 hours and the bactericidal level

The bactericidal activity of ristocetin is apparently not restricted to actively dividing cells [11] The activity of the antibiotic was determined against cells from 3 and 24 hour cultures of *Staph aureus* MIH 2 The data presented in table IV indicate no striking differences in the rate of killing cells from the

TABLE III

Bactericidal Action of Ristocetin against *Staph albus* 3519

Incubation time hr	Ristocetin concentration µg/ml			
	32*	16†	8	0 (control)
Number of viable cells per ml				
0	1[illegible]2 000	111 500	111 000	106 500
2	51 000	105 500	116 500	239 500
4	1 290	11 [illegible]00	105 500	4 0 0 000
6	255	1 070	85 000	16,500 000
24	<5	1 385	9 950 000	560 000 000

Minimum inhibitory concentration of 48 hour test
† Minimum inhibitory concentration of 24 hour test.
Reprinted with permission from Grundy et al

TABLE II

Ristocetin Minimum Inhibitory Concentrations for 235 Microorganisms*
(Tube Dilution Method)

Ristocetin in Vitro Sensitivity Tests with 74 Strains of D pneumoniae

No of strains	µg/ml	Lot no
9	0 2–1 0	E 5330
23	2 0–3 0	(purity 500 µg/mg)
27	0 2–0 5	E 5626
2	1 0–2 0	(purity 774 µg/mg)
1	<0 1–0 1	E 5903
12	0 2–0 5	(purity 863 µg/mg)

Ristocetin in Vitro Sensitivity Tests with 56 Strains of Coagulase positive Micrococcus pyogenes *var* aureus

No of strains	µg/ml	Lot no
3	4 0– 5 0	E 5330
14	10 0–14 0	(purity 500 µg/mg)
4	20 0–50 0	
13	2 0– 3 0	E 5626
14	4 0– 5 0	(purity 774 µg/mg)
7	2 0– 3 0	E 5903
1	4 0– 5 0	(purity 863 µg/mg)

Ristocetin in Vitro Sensitivity Tests with 90 Strains of Streptococci

Group A β streptococci	α hemolytic *Streptococcus viridans*	*Enterococcus*	µg/ml	Lot no
4	1	5	<0 1– 0 3	E 5330
9	1	2	1 0– 5 0	(purity 500 µg/mg)
		9	6 0– 8 0	
		6	10 0–20 0	
7	2	1	<0 1– 0 5	E 5626
1	4	6	1 0– 5 0	(purity 774 µg/mg)
	1	3	10 0–20 0	
7	2	7	<0 1– 0 5	E 5903
1	3	5	1 0– 5 0	(purity 863 µg/mg)
	1	2	10 0–20 0	

Table II Continued on Page 143

and *Streptococcus mitis* Schneierson et al [9] arrived at essentially the same conclusion using a different technique

STUDIES OF BACTERIAL RESISTANCE TO RISTOCETIN

Grundy et al [11] in a study of more than 400 cultures of streptococci staphylococci and pneumococci found none naturally resistant to ristocetin These were largely isolates from three hospital laboratories and included many cultures that were resistant to one or more of the commercially available antibiotics

Bacteria do not readily acquire resistance to ristocetin in vitro In the early studies using a crude preparation Grundy et al[11] were unsuccessful in their attempts to develop significant resistance Both the conventional serial transfer technique and the Szybalski gradient plate technique were used in their experiments and six cultures of staphylococci were tested with each technique All staphylococci were recent isolates from clinical specimens and several were resistant to one or more of the commercially available antibiotics No marked increase in resistance was observed with either of these series of transfers An eightfold increase in resistance was the highest attained and this occurred in only one strain

Subsequently comparative studies were carried out with crystalline preparations of ristocetins A and B using a strain of *Staph albus* two strains of *Staph aureus* and two strains of enterococcus None of the cultures acquired marked resistance in 20 serial transfers An eightfold increase in tolerance was the greatest change observed and resistance appeared to develop more slowly to ristocetin B than to ristocetin A or to a combination of both Again the eightfold increase was attained in only one of the strains

Romansky et al [8] in a preliminary report studied the development of resistance to ristocetin by the serial tube dilution subculture method Two strains of *Staph aureus* were used both of which had been isolated originally from purulent exudates A comparison was made between ristocetin penicillin and erythromycin No significant resistance to ristocetin developed in these two strains after 45 subcultures By way of contrast the organisms showed a 40 to 100 fold increase in tolerance to penicillin by the fourteenth subculture One of the strains showed a tenfold and the other a 100 fold increase in tolerance to erythromycin by the eighteenth subculture

Hsie et al [15] using an agar gradient technique showed that staphylococci slowly develop a low order of resistance to ristocetin Measuring antibiotic effect in terms of threshold concentration * they were able to induce only

Hsie et al defined "threshold concentration" of an antibiotic as the concentration at which the greatest majority of a bacterial population succumb to it, and only a small fraction of the population, say one or a few in millions or so can survive and grow to develop visible colonies "

younger culture were destroyed only slightly faster than cells from the 24 hour culture

The same authors found that ristocetin displayed bactericidal activity *against the H_{37} Rv strain of human Mycobacterium tuberculosis* After two weeks incubation in a medium containing polysorbate 80 the bacteriostatic concentration was found to be 2 to 4 μg /ml The bactericidal concentration designated as failure of growth three weeks after subculture was 8 to 16 μg /ml After prolonged incubation the bacteriostatic concentration was found to rise to levels approaching 8 to 16 μg /ml

In our initial studies we observed a narrow range between bacteriostatic and bactericidal effect against pneumococci streptococci, and staphylococci As laboratory data have accumulated however some strains have shown a greater variability in this range Nonetheless in studies employing both tube and pour plate subculture techniques it appears that the majority of the microorganisms will be bactericidally affected at levels close to the minimum inhibitory concentration In relation to clinical applications this would explain the successful results obtained without maintaining blood levels at the maximum bactericidal point

Geraci[10] citing data of Heilman noted a wider range between bacteriostatic and bactericidal effect in some strains of staphylococci enterococci

TABLE IV

Comparative Bactericidal Action of Ristocetin against a 3 Hour and a 24 Hour Culture of *Staph aureus* MIH 2

Incubation time hr	Ristocetin concentration μg /ml			
	32	16	8	0
	Log of numbers of viable cells per ml			
0	5 9 (5 7)†	6 0 (5 7)	6 1 (5 7)	5 9 (5 8)
2	4 6 (4 6)	4 4 (4 5)	4 7 (4 6)	7 2 (6 5)
4	3 0 (3 9)	3 3 (3 9)	3 5 (3 8)	8 0 (7 7)
6	2 5 (3 1)	2 6 (3 2)	2 8 (3 3)	8 9 (8 4)
24	approx 0 7 (approx 1 0)	approx 1 3 (2 9)	4 8 (5 8)	9 6 (9 2)
48	<0 7 (<0 7)	<0 7 (<0 7)	9 1 (9 0)	9 0 (9 4)

* Three hour culture
† Twenty four hour culture
Reprinted with permission from Grundy et al.[21]

and *Streptococcus mitis* Schneierson et al [9] arrived at essentially the same conclusion using a different technique

STUDIES OF BACTERIAL RESISTANCE TO RISTOCETIN

Grundy et al [11] in a study of more than 400 cultures of streptococci staphylococci and pneumococci found none naturally resistant to ristocetin These were largely isolates from three hospital laboratories and included many cultures that were resistant to one or more of the commercially available antibiotics

Bacteria do not readily acquire resistance to ristocetin in vitro In the early studies using a crude preparation Grundy et al[11] were unsuccessful in their attempts to develop significant resistance Both the conventional serial transfer technique and the Szybalski gradient plate technique were used in their experiments and six cultures of staphylococci were tested with each technique All staphylococci were recent isolates from clinical specimens and several were resistant to one or more of the commercially available antibiotics No marked increase in resistance was observed with either of these series of transfers An eightfold increase in resistance was the highest attained and this occurred in only one strain

Subsequently comparative studies were carried out with crystalline preparations of ristocetins A and B using a strain of *Staph albus* two strains of *Staph aureus* and two strains of enterococcus None of the cultures acquired marked resistance in 20 serial transfers An eightfold increase in tolerance was the greatest change observed and resistance appeared to develop more slowly to ristocetin B than to ristocetin A or to a combination of both Again the eightfold increase was attained in only one of the strains

Romansky et al [28] in a preliminary report studied the development of resistance to ristocetin by the serial tube dilution subculture method Two strains of *Staph aureus* were used both of which had been isolated originally from purulent exudates A comparison was made between ristocetin penicillin and erythromycin No significant resistance to ristocetin developed in these two strains after 45 subcultures By way of contrast the organisms showed a 40 to 100 fold increase in tolerance to penicillin by the fourteenth subculture One of the strains showed a tenfold and the other a 100 fold increase in tolerance to erythromycin by the eighteenth subculture

Hsie et al [15] using an agar gradient technique showed that staphylococci slowly develop a low order of resistance to ristocetin Measuring antibiotic effect in terms of threshold concentration * they were able to induce only

* Hsie et al defined threshold concentration of an antibiotic as "the concentration at which the greatest majority of a bacterial population succumb to it, and only a small fraction of the population say one or a few in millions or so can survive and grow to develop visible colonies.

younger culture were destroyed only slightly faster than cells from the 24 hour culture

The same authors found that ristocetin displayed bactericidal activity against the H_{37} Rv strain of human *Mycobacterium tuberculosis* After two weeks incubation in a medium containing polysorbate 80 the bacteriostatic concentration was found to be 2 to 4 µg/ml The bactericidal concentration designated as failure of growth three weeks after subculture was 8 to 16 µg/ml After prolonged incubation the bacteriostatic concentration was found to rise to levels approaching 8 to 16 µg/ml

In our initial studies we observed a narrow range between bacteriostatic and bactericidal effect against pneumococci streptococci and staphylococci As laboratory data have accumulated however some strains have shown a *greater variability in this range Nonetheless in studies employing both tube* and pour plate subculture techniques it appears that the majority of the microorganisms will be bactericidally affected at levels close to the minimum inhibitory concentration In relation to clinical applications this would explain the successful results obtained without maintaining blood levels at the maximum bactericidal point

Geraci[10] citing data of Heilman noted a wider range between bacteriostatic and bactericidal effect in some strains of staphylococci, enterococci,

TABLE IV

Comparative Bactericidal Action of Ristocetin against a 3 Hour and a 24 Hour Culture of *Staph aureus* MIH 2

Incubation time hr	Ristocetin concentration µg/ml			
	32	16	8	0
Log of numbers of viable cells per ml				
0	5.9* (5.7)†	6.0 (5.7)	6.1 (5.7)	5.9 (5.8)
2	4.6 (4.6)	4.4 (4.5)	4.7 (4.6)	7.2 (6.5)
4	3.0 (3.9)	3.3 (3.9)	3.5 (3.8)	8.0 (7.7)
6	2.5 (3.1)	2.6 (3.2)	2.8 (3.3)	8.9 (8.4)
24	approx 0.7 (approx. 1.0)	approx 1.3 (2.9)	4.8 (5.8)	9.6 (9.2)
48	<0.7 (<0.7)	<0.7 (<0.7)	9.1 (9.0)	9.0 (9.4)

* Three hour culture
† Twenty four hour culture
Reprinted with permission from *Grundy et al*[11]

The dosages of ristocetin required to provide various degrees of protection were determined for the three test infections Experiments were carried out employing a combination of ristocetin and gamma globulin in amounts that individually were minimally effective The results are summarized in table VII

In all cases the combination of gamma globulin and ristocetin produced a greater 10-day survival than did either agent alone The effectiveness of gamma globulin in enhancing the in vivo effect of ristocetin appeared to be greatest in streptococcal infections next in staphylococcal and least in pneumococcal It is of interest that gamma globulin exhibited a definite effect in

TABLE VI

Treatment of Mice Infected with Streptococci by Gamma Globulin Only

Calculated LD_{50} streptococci injected	Control (no gamma globulin)	Dilution of gamma globulin 1/20	1/40	1/80
1	50*	100	90	100
10	10	70	90	80
100	0	50	50	70
1000	0	20	40	20
10 000	0	0	0	0

Treatment of Mice Infected with Staphylococci by Gamma Globulin

Calculated LD_{50} staphylococci injected	Control (no gamma globulin)	Dilution of gamma globulin 1/20	1/40	1/80
1	70*	100	100	100
10	0	100	70	70
100	0	60	20	10
1000	0	20	10	0

Treatment of Mice Infected with Pneumococci by Gamma Globulin

Calculated LD_{50} pneumococci injected	Control (no gamma globulin)	Dilution of gamma globulin 1/20	1/40	1/80
1	60	60	80	60
10	10	0	20	10
100	0	0	0	0
1000	0	0	0	0

* Per cent survivors 10 days postinfection
Reprinted with permission from Holper et al

TABLE V

The Efficacy of the Ristocetins in the Treatment of Infected Mice

Organism	Ristocetin A			Ristocetin B		
	Total dose mg /Kg	Survivors 10 days after infection		Total dose mg /Kg	Survivors 10 days after infection	
		No	%		No	%
Str pyogenes	0 87	0/20	0	0 58	6/20	30
C203 1000 to 10 000	1 7	4/20	20	0 96	10/10	100
LD_{50}	2 9	16/20	80	1 2	18/20	90
	3 5	18/20	90	1 9	16/19	84
	5 8	20/20	100	2 3	20/20	100
Staph aureus	2 9	3/20	15	1 9	5/20	25
Smith 100 to 1000	5 8	9/20	45	3 8	12/20	60
LD_{50}	11 5	13/20	65	7 7	20/20	100
D pneumoniae	2 9	3/10	30	1 9	12/20	60
ATCC 6301 1000 to	5 8	4/20	20	3 8	17/19	89
10 000 LD_{50}	11 5	17/20	85	7 7	20/20	100
	23 0	9/10	90			

Reprinted with permission from Grundy et al [13]

a fivefold increase in resistance to ristocetin in 10 passages This entailed a change in the threshold concentration from 1 5 µg /ml to a final concentration of 7 5 µg /ml Similar studies revealed an 1100 fold increase in resistance to novobiocin in five steps and a 1000 fold increase in resistance to oleandomycin in three steps

In Vivo Studies Grundy et al[13] found that ristocetin was active in mouse protection tests Mice were infected intraperitoneally with either *Streptococcus pyogenes Staph aureus* or *D pneumoniae* and then were given three equal intramuscular doses of ristocetin one three and six hours later The results of their investigations using purified ristocetins A and B separately revealed that ristocetin B is about three times as effective as ristocetin A in vivo The data from their experiments are presented in table V Their preliminary studies in mouse tuberculosis indicated that ristocetin has little or no therapeutic effect in this disease

After a report that human gamma globulin enhances the activity of chloramphenicol,[8] Holper et al[14] studied the effect of gamma globulin on the activity of ristocetin in experimental mouse infections Preliminary studies using gamma globulin alone indicated that it had approximately equal protective activity in streptococcal and staphylococcal infections In contrast gamma globulin had no effect on pneumococcal infections at any concentrations of pneumococci or gamma globulin dosage studied These results are summarized in table VI

doses of 100 mg /Kg while doses of 2 5 to 50 mg /Kg were generally well tolerated by dogs Single oral doses of 300 mg /Kg produced no effects in cats or dogs

Chronic toxicity studies in rabbits revealed that dosages up to 200 mg /Kg administered intravenously every day for two to four weeks produced no toxicity No animal showed disturbances in vestibular function Similar studies in dogs given up to 100 mg /Kg for two to nine weeks revealed no adverse effects Rabbits tolerated 1 mg /Kg intracisternally The intramuscular injection of ristocetin was regularly attended by slight to moderate reaction at the injection site least with a 2 per cent and greatest with a 5 per cent solution Intravenous administration of 5 to 50 mg /Kg to anesthetized dogs had no consistent effect on blood pressure respiration or intestinal motility

Hwang et al[16] also studied the distribution and excretion of ristocetin in animals Single doses of 10 mg /Kg administered to dogs intravenously were followed within the first hour by blood levels of 25 to 60 μg /ml Levels gradually fell over the next eight hours to 2 5 to 5 0 μg /ml

Despite the fact that ristocetin dialyzes poorly through cellophane membranes it diffuses rapidly into the lymph and equilibrium takes place in 15 to 30 minutes Almost no antibiotic activity is found in the bile cerebrospinal fluid aqueous humor or saliva of the dog when the level in the blood is between 5 and 10 μg /ml

After a single 10 mg /Kg dose of ristocetin the recovery rate from the urine amounted to approximately 30 per cent during the first four hours 45 per cent after eight hours and about 80 per cent in 24 hours The renal clearance rate of ristocetin A in dogs was about 65 per cent of the glomerular filtration rate as measured by simultaneous clearance of creatinine

Ristocetin administered orally to dogs in a 5 per cent solution (100 200 and 300 mg /Kg) was recovered in the urine to the extent of 0 1 to 0 6 per cent in five hours and 0 3 to 1 per cent in 24 hours Rats given ristocetin orally at dosage levels of 1 2 and 4 Gm /Kg have urinary excretions of 0 4 per cent of the 1 Gm /Kg dose and about 1 per cent of the 2 and 4 Gm /Kg dose in 24 hours

Hwang et al[16] concluded that ristocetin is relatively low in toxicity when administered by a variety of routes and is relatively inert from a pharmacodynamic standpoint Intravenous administration produces prolonged blood levels When administered orally ristocetin is very poorly absorbed The major route of excretion for parenterally administered ristocetin is through the kidney

Human Studies In early studies Romansky et al[28] found that the intramuscular administration of ristocetin in doses of 200 to 500 mg was quite painful and that blood levels attained by this route of administration were generally less than 5 μg /ml

TABLE VII

Gamma Globulin plus Ristocetin

Ristocetin mg /Kg	Per cent survivors after 10 days — Ristocetin only	Per cent survivors after 10 days — Ristocetin plus gamma globulin
Treatment of Mice Infected with Streptococci by Ristocetin plus Gamma Globulin*		
1 65	70	95
1 1	45	70
0 55	55	90
0 275	0	35
0 1375	0	10
Gamma globulin alone (0 5 ml of 1/20 dilution) per cent survivors 0		
Treatment of Mice Infected with Staphylococci† by Ristocetin plus Gamma Globulin		
2 2	90	100
1 1	70	80
0 55	30	67
0 275	20	20
0 1375	7	37
Gamma globulin alone (0 5 ml of 1/40 dilution) per cent survivors 20		
Treatment of Mice Infected with Pneumococci‡ by Ristocetin plus Gamma Globulin		
2 2	70	60
1 1	15	35
0 55	5	30
0 275	0	30
0 1375	0	10
Gamma globulin alone (0 5 ml of 1/20 dilution) per cent survivors 0		

* 10 LD_{50} of *Str pyogenes*
† 10^3 LD_{50} *Staph aureus*
‡ 10^3 LD_{50} *D pneumoniae*
Reprinted with permission from Holper et al [14]

pneumococcal infections when combined with the antibiotic although it exhibited no effect when used alone

PHARMACOLOGY

Animal Experiments Acute toxicity studies by Hwang et al[16] revealed that the LD_{50} for mice and rats given ristocetin intravenously varied from 780 to 1820 mg /Kg depending on the rapidity of injection (95 per cent confidence limits) Mice tolerated 1 Gm /Kg subcutaneously and 5 5 to 12 5 Gm /Kg orally without difficulty Occasional animals given massive intravenous doses at or close to the LD_{50} level (by slow injection method) showed slight dilation of the renal tubules and round cell infiltration in the renal parenchyma This renal effect was apparently absent at lower dosages The acute effects after lethal doses were coma and respiratory failure, occurring a few minutes to a few hours later Rabbits tolerated repeated intravenous

doses of 100 mg /Kg while doses of 2 5 to 50 mg /Kg were generally well tolerated by dogs Single oral doses of 300 mg /Kg produced no effects in cats or dogs

Chronic toxicity studies in rabbits revealed that dosages up to 200 mg /Kg administered intravenously every day for two to four weeks produced no tox icity No animal showed disturbances in vestibular function Similar studies in dogs given up to 100 mg /Kg for two to nine weeks revealed no adverse effects Rabbits tolerated 1 mg /Kg intracisternally The intramuscular injec tion of ristocetin was regularly attended by slight to moderate reaction at the injection site least with a 2 per cent and greatest with a 5 per cent solution Intravenous administration of 5 to 50 mg /Kg to anesthetized dogs had no consistent effect on blood pressure respiration or intestinal motility

Hwang et al[16] also studied the distribution and excretion of ristocetin in animals Single doses of 10 mg /Kg administered to dogs intravenously were followed within the first hour by blood levels of 25 to 60 μg /ml Levels gradu ally fell over the next eight hours to 2 5 to 5 0 μg /ml

Despite the fact that ristocetin dialyzes poorly through cellophane mem branes it diffuses rapidly into the lymph and equilibrium takes place in 15 to 30 minutes Almost no antibiotic activity is found in the bile cerebrospinal fluid aqueous humor or saliva of the dog when the level in the blood is between 5 and 10 μg /ml

After a single 10 mg /Kg dose of ristocetin the recovery rate from the urine amounted to approximately 30 per cent during the first four hours 45 per cent after eight hours and about 80 per cent in 24 hours The renal clear ance rate of ristocetin A in dogs was about 65 per cent of the glomerular filtra tion rate as measured by simultaneous clearance of creatinine

Ristocetin administered orally to dogs in a 5 per cent solution (100 200 and 300 mg /Kg) was recovered in the urine to the extent of 0 1 to 0 6 per cent in five hours and 0 3 to 1 per cent in 24 hours Rats given ristocetin orally at dosage levels of 1 2 and 4 Gm /Kg have urinary excretions of 0 4 per cent of the 1 Gm /Kg. dose and about 1 per cent of the 2 and 4 Gm /Kg dose in 24 hours

Hwang et al[16] concluded that ristocetin is relatively low in toxicity when administered by a variety of routes and is relatively inert from a pharmaco dynamic standpoint Intravenous administration produces prolonged blood levels When administered orally ristocetin is very poorly absorbed The major route of excretion for parenterally administered ristocetin is through the kidney

Human Studies In early studies Romansky et al[28] found that the intramus cular administration of ristocetin in doses of 200 to 500 mg was quite painful and that blood levels attained by this route of administration were generally less than 5 μg /ml

In a more recent study by Dries et al [9] ristocetin was administered intra muscularly to 8 children up to 15 years of age in a dosage of 25 mg /kg body weight Five mg of cortisone was added to each dose Serum concentrations of 5 3 to 21 2 μg /ml were recorded at two hours and remained as high as 2 6 to 10 0 μg /ml even after 12 hours Spinal fluid content in these patients was less than 0 7 μg /ml There were no side reactions even though 2 patients were treated for 10 and 11 days respectively with injections every six to eight hours Careful observation will be required in the repeated administration of this amount of steroid to children

The intravenous route is the method currently favored for the administration of ristocetin The dose to be given may be dissolved in approximately 100 ml of 5 per cent glucose solution or hypotonic or normal saline The antibiotic solution is injected over a 5 to 30 minute period

After the administration of 1 Gm intravenously ristocetin levels in the serum at one to two hours will range between 5 and 40 μg /ml depending on the speed of administration When the dose is increased to 2 Gm , blood levels at one to two hours may be as high as 80 μg /ml The concentration falls gradually to levels between 10 and 20 μg /ml at 12 hours and may be as high as 5 μg /ml even after 24 hours [6]

The blood levels obtained in cumulative studies [8] with various dosage sched ules are shown in table VIII It should be borne in mind that at the time of this study ristocetin was administered in a larger volume of solution and over a longer period of time than is now recommended

Dries and co workers[3] also studied the intravenous administration of ris tocetin in children Two hours after a dose of 12 5 mg /kg was administered rapidly serum levels varied from 1 3 to 10 6 μg /ml Thereafter the level declined gradually to 0 7 μg /ml or less at 12 hours After the intravenous administration of 25 mg /kg the content of the serum after one hour was 21 2 μg /ml thereafter gradually decreasing so that 12 hours later the levels ranged between 0 7 and 10 6 μg /ml

Ristocetin diffuses freely into pleural and ascitic fluids levels at two to four hours approximate those in the blood when 1 to 2 Gm is administered rapidly intravenously [6] As noted in table VIII pleural fluid concentrations three or four hours after a 500 mg dose approximate those in the blood

Studies of spinal fluid levels revealed concentrations of less than 0 625 μg /ml [8] three hours after a 1 Gm dose despite concentrations in the blood determined simultaneously that ranged between 5 and 20 μg /ml A 2 Gm dose administered to 6 patients resulted in serum levels between 20 and 80 μg /ml at two hours but the spinal fluid level in 4 of these patients was only 5 μg /ml Another patient had a spinal fluid level of 0 625 μg /ml at a time when the concentration in the serum was 80 μg /ml

Kanner[17] has demonstrated that the passage of ristocetin across the blood

TABLE VIII

Ristocetin Serum Concentrations after Cumulative Intravenous Administration

Dosage	Hours after at least 4 doses	Serum level µg /ml	No of blood samples
250 mg every 6 hr	4	5	1
250 mg every 4 hr	4	5	1
500 mg every 8 hr	2	5–20	3
	6	5	1
	8	2 5	1
	12	2 5	1
500 mg. every 6 hr	1	40	1
	2	40	1
	4	5–20	2
	5	2 5	1
	6	20	5
	8	1 25	1
	(pleural fluid at 3 and 4 hr 10 µg /ml)		
	(spinal fluid at 3 hr no level)		
1000 mg every 12 hr	8	10	1
	12	5–2 5	2
	14	10	1
1000 mg every 8 hr	8	10–40	3
	18	5	1
1000 mg every 6 hr	4	40	1
	5	20	1
	6	20	1
	8	10–20	2
	10	10	1

brain barrier may be enhanced in meningitis Spinal fluid concentrations of 0 32 µg /ml were attained at serum concentrations ranging from 0 64 to 10 24 µg /ml during treatment of a patient with staphylococcal brain abscess and meningitis During treatment of a patient of our own with staphylococcal brain abscess and meningitis with ristocetin spinal fluid levels of 1 25 to 2 5 µg /ml were recorded at serum concentrations of 40 to 80 µg /ml [7]

Further studies are needed to ascertain whether diffusion occurs across the placenta and into bile milk or seminal fluid Excretion studies reveal that 45 to 50 per cent of a 1 to 2 Gm dose is recoverable in the urine in 24 hours [6]

Oral ristocetin in dosages of 2 to 4 Gm does not reduce the total bacterial count in the stools but does reduce the number of enterococci and staphylococci No inhibitory effect on yeast or yeastlike organisms has been observed [6]

Cohn and Longacre[4] administered 200 mg of ristocetin together with 500 mg of neomycin every hour for four hours then every six hours for a total of 72 hours in studies of preoperative bowel preparation Marked suppression of treptococci staphylococci and coliform organisms occurred Yeasts were unaffected by this therapy Similar results were obtained by Shidlovsky and

Prigot[31] who gave 4 Gm each of ristocetin and neomycin daily in divided doses

We have found that ristocetin solutions containing 1 mg /ml of antibiotic are well tolerated by the tracheobronchial tree when used for nebulization therapy for as long as two weeks

DOSAGE AND ROUTES OF ADMINISTRATION

Ristocetin is commercially available as a sterile lyophilized powder in vials containing a mixture of ristocetins A and B representing 500 mg of ristocetin A activity The dosage of ristocetin is 25 to 50 mg /Kg /day depending on the type of infecting microorganism and the severity of the disease

For intravenous administration a 0 5 to 1 0 per cent solution should be prepared using about 100 ml of 5 per cent glucose or normal or hypotonic saline This amount is given over a period of 5 to 30 minutes and may be injected directly into a vein or into the tubing of an intravenous infusion used for fluid therapy Solutions should be prepared so that the maximum concentration of antibiotic does not exceed 25 mg /ml

Generally 0 5 to 1 0 Gm is administered at 12 hour intervals in adults This represents approximately 25 mg /Kg /day In more severe infections particularly those caused by the *Staphylococcus* including bacterial endocarditis and deep seated lesions 1 or more Gm every eight hours may be required When renal function is compromised the dosage should be reduced to avoid excessive accumulation of the antibiotic in the body For pediatric patients the dosage and schedules are the same as for adults 25 to 50 mg /Kg /day

Ristocetin has been used for preoperative bowel preparation by Cohn and Longacre[4] who used a combination of 200 mg ristocetin and 500 mg neomycin every hour for four hours then every six hours for a total of 72 hours Shidlovsky and Prigot[31] achieved the same results by administering 1 Gm of each antibiotic every six hours for 24 hours

Nebulization therapy with ristocetin appears to be of benefit in staphylococcal lung abscess We employ a solution containing 1 mg /ml

SIDE EFFECTS

The analysis of side effects is based on data from published reports[3, 6, 9, 17, 18, 1, 5, 27, 8, 30, 3, 34] of 139 patients who were treated with ristocetin Side effects were noted in 29 or 20 8 per cent Hematological side effects were encountered in 18 or 12 9 per cent Varying degrees of leukopenia neutropenia thrombocytopenia and eosinophilia occurred either alone or in combination Other side effects that were observed included phlebitis in 8 instances fever in 8 maculopapular eruption in 4 and gastrointestinal symptoms in 2

Table IX summarizes the hematological changes that were described It is of interest that 13 of the 18 patients with hematological side effects received a maximum daily dosage of 3 Gm or more at one time or another during therapy suggesting that the incidence of these side effects may be related to high daily dosage levels Although high daily dosage levels may be associated with side effects in individual cases 27 other patients in this series of 139 who also were given 3 Gm or more per day had no side effects Hematological effects were infrequent at dosage levels lower than 3 Gm /day occurring in only 4 instances They also occurred in a patient with severe uremia receiving less than 3 Gm /day There is some difficulty in assessing the hematological effects of ristocetin in some patients since the nature of associated illnesses could also affect the blood picture The series reported by Gangarosa et al [9] for instance included 2 patients with severe uremia a patient with pre-existing bone marrow aplasia and a patient with acute disseminated lupus erythematosus who simultaneously received chloramphenicol and erythromycin

The results of bone marrow examination were reported in 5 cases and were essentially normal in all but 1 patient in whom eosinophilia was noted This suggests that ristocetin exerts its effect on the circulating blood elements rather than on the bone marrow

It is desirable that hemoglobin estimation leukocyte differential and platelet counts be done on alternate days in adults receiving more than 2 Gm /day or children receiving more than 25 mg /Kg /day At lower dosages twice weekly determinations are probably adequate In the presence of azotemia more frequent blood counts are indicated If the blood urea nitrogen rises during therapy the dosage of ristocetin should be reduced

Phlebitis occurred in 8 instances In our experience this side effect is related to the administration of large volumes of antibiotic solution and extended periods of infusion Administration as recommended will minimize this side effect.

The exact cause of fever and rash noted in 8 and 4 instances respectively is not clear A causal relationship between ristocetin and fever was not clear in several of the cases [34] in other patients several antibiotics were administered simultaneously It is evident from evaluation of this series that the status of renal function is important for when it is impaired concentrations in the blood tend to rise It would also appear that in individual cases the occurrence of hematological side effects is probably related to high antibiotic concentrations in the blood Since relatively crude preparations were used in the early clinical studies impurities may be a factor in the occurrence of these side effects None of the deaths in this series appear to be directly attributable to ristocetin All the side effects were found to be reversible by either reducing the dosage or stopping therapy

TABLE IX

Ristocetin—139 Reported Cases Hematological Changes

Age yr	Sex	Diagnosis	Hematology
42	M	*Subacute bacterial endocarditis (enterococcal)*	*Leukopenia neutropenia*
27	F	Subacute bacterial endocarditis (enterococcal)	Leukopenia neutropenia
14	M	Cervical abscess	Leukopenia neutropenia eosinophilia
67	M	Sepsis (staphylococcal)	Leukopenia neutropenia eosinophilia
32	F	Subacute bacterial endocarditis (staphylococcal)	Leukopenia neutropenia eosinophilia
21	F	Subacute bacterial endocarditis (staphylococcal)	Leukopenia neutropenia eosinophilia platelet depression
21	M	Pneumonia (staphylococcal)	Platelet depression
26	M	Pneumonia (staphylococcal)	Platelet depression
43	M	Subacute bacterial endocarditis (enterococcal)	Thrombocytopenia
36	M	Renal insufficiency (uremia) sepsis (staphylococcal)	Thrombocytopenia leukopenia
26	M	Pancytopenia hypoplastic bone marrow pneumonia (staphylococcal)	Neutropenia platelet depression
50	M	Renal insufficiency (uremia) sepsis (staphylococcal)	Thrombocytopenia
38	F	Lupus erythematosus sepsis	Anemia (due to drug?)
9 weeks	M	Periorbital cellulitis	Neutropenia
35	F	Bronchopneumonia	Thrombocytopenia
40	F	Lobar pneumonia	Thrombocytopenia
33	M	Bronchopneumonia	Leukopenia
26	M	*Subacute bacterial endocarditis* (staphylococcal)	*Leukopenia*

All side effects reversible on reduction or withdrawal of drug.

TABLE IX

18 Cases Relation to Maximum Daily Dosage

Maximum daily dosage		Total dose	Duration of treatment	
Gm	*mg /Kg*	*Gm*	days	Reference
3 0	50	70	24	9 27
2 5	40	22 5	9	9 27
2 5	?	30	15	22
4 0	?	44	12	22
4 5	?	44	13	34
4 0	About 70	42	17	34
3 0	41 4	20	19	30
3 0	41 4	33	15	30
4 5	75	23 5	8	9
3 0	40	15	7	9
3 0	35	42	14	9
2 25 3 0	30 40	8 12	7 4	9
9 0	225 0	57	11	9
0 150	30	1 75	5	9
1 5	?	7 5	5	2
1.5	?	4 5	3	2
3 0	?	25 0	9–?	2
3.5	43	30	11	33

TABLE X

Ristocetin—Results of Therapy in Staphylococcal Infections

	Number	Cured	Improved	Failed	Other out come*	Reference
Pneumonia, lung abscess	40	30	2	2	6	3 7 9 30 37
Skin and soft tissues	19	13	6			3 7 21 32
Osteomyelitis arthritis	11	3	8			3 21 30 32
Endocarditis	7	5		2		5 25 27 33 34
Septicemia	8	3	2	2	1	9 18 22 33
Meningitis brain abscess	2	2				7 17
Visceral	2	1	1			7 32
Total	89	57	19	6	7	

* Died of unrelated causes or before therapy could be evaluated

THERAPY OF STAPHYLOCOCCAL INFECTIONS

In addition to its efficacy in pneumococcal and streptococcal infections ristocetin has made possible the short term therapy of enterococcal endocarditis[27]

One hundred and thirty nine cases of ristocetin treated infections have been collected from the literature[3, 5, 7, 9, 17, 18, 1 5, 7, 30, 32, 34] Eighty nine of these were found to have a clearly established staphylococcal etiology[3, 5, 7, 9, 17, 18, 1 27, 30, 32, 34] The number and distribution of cases along with the author s evaluation of the data are summarized in table X

Pulmonary Infections[3, 7, 9, 30, 32] While staphylococcal pulmonary infections may occur as primary processes they are more often seen as complications of septicemia or as superinfections in such conditions as influenzal or bacterial pneumonia They may also emerge in the course of antibiotic therapy for other pulmonary conditions especially if therapy is prolonged

Forty of the staphylococcal infections recorded in the literature involved the lungs or pleural space (table X) All but a few patients were seriously ill as the following case report indicates Moreover all but 7 had previously received other antibiotics without apparent effect Ristocetin was considered to have a curative effect in 30 or 75 per cent 2 were improved Antibiotic therapy failed in 2 and 6 died of unrelated causes or before therapy could be evaluated The nature of these staphylococcal infections is such that one would generally expect a response by lysis rather than by crisis The 7 patients treated with ristocetin alone had a uniformly good response indicating that ristocetin is effective as a primary agent in the therapy of staphylococcal pulmonary infections Patient 25 of Schumacher et al[30] demonstrates an example of the type of pulmonary infection for which ristocetin was given

A 29 year old civilian technician was the only survivor of the accidental explosion of several Nike" missiles He suffered 40 per cent second and third degree burns and after six days of treatment was transferred to this hospital Fever of 104 to 105 F did not remit with penicillin streptomycin and chloramphenicol On the fourth hospital day a roentgenogram revealed bilateral pneumonitis On the seventh hospital day operative débridement was carried out. The next day jaundice was present temperature was 106 F and sputum culture revealed coagulase positive hemolytic *Staph aureus* Ristocetin 19 4 mg /Kg /day was started intravenously and other antimicrobials were discontinued Temperature fell by lysis and jaundice subsided The patient had an uneventful recovery Roentgenographic examination of the chest on the twenty second hospital day was negative

The dosage in this patient averaged 1 5 Gm /day while the over all range of dosage was 1 to 3 Gm /day in this series [30] Terry and Bradley[32] generally employed 3 to 4 Gm /day initially with subsequent decrease in dosage while Romansky[7] generally administered 2 to 3 Gm /day Gangarosa et al[9] used 3 Gm /day in their 3 patients with subsequent reduction in 1 case to 2 Gm /day

From evaluating the dosage schedules in these cases it appears that an initial dosage of 25 to 50 mg /Kg /day (generally 3 Gm /day in adults) followed by a reduction to 20 to 25 mg /Kg /day (approximately 2 Gm /day) is to be recommended It is also obvious that adjunctive measures such as bronchoscopy or drainage of empyema are as important as antibiotic therapy

Judging from the experience summarized in table X ristocetin can be used effectively as the sole agent in the therapy of staphylococcal pulmonary infections

Skin and Soft Tissue Infections [3 7 21 3] The 19 patients (table X) comprising this group had widespread furunculosis multiple abscesses or involvement of deeper structures such as bursae Ristocetin was credited with cure in 13 cases and definite improvement occurred in the remainder Ten of the patients were treated with ristocetin alone while the remainder responded to ristocetin after other antibiotics had failed to eradicate the infection

The majority of these patients were given 2 Gm /day with an occasional patient being given 3 or more Gm initially Case 9 of Bush[3] illustrates the rapid response obtained in treating this type of infection

A 51 year old man developed an extensive cellulitis in 24 hours from a small pimple on his left cheek His temperature rose to 103 F The causative organism proved to be coagulase positive hemolytic *Staphylococcus* The blood culture was positive A diffuse glandular enlargement appeared over the entire left neck He received 1 5 Gm of ristocetin twice daily for a total of 16 5 Gm His temperature rose to a height of 104 F but on the fifth day returned to normal

The good result obtained in this patient with cellulitis is impressive in view of the concomitant bacteremia Other cases reviewed included abscesses in these the improvement was definite though not so dramatic The effect of

adjunctive measures such as hot soaks shaving hairy areas, surgical drainage, and the use of soaps containing antibacterial agents such as hexachlorophene cannot be evaluated from the cases described but the effect of ristocetin seems clear This is not to discount these other measures, for pus will probably always be an indication for surgical intervention

For skin and soft tissue infections dosage schedules of 20 to 25 mg/kg/day or about 2 Gm/day for an adult are adequate

Osteomyelitis and Septic Arthritis [3 1 30 3] Osteomyelitis is a feared complication of trauma and sepsis Very often the infection has advanced to the stage of an indolent, walled off focus surrounded by avascular tissue before it is discovered

Ristocetin has shown promise as a primary agent in the treatment of staphylococcal osteomyelitis especially when antibiotic therapy is combined with appropriate surgical procedures The results of therapy in the 11 cases summarized in table X are encouraging for in 1 patient critically ill with septic arthritis reported by Terry and Bradley[32] and 2 with osteomyelitis described by Miller et al [1] and Schumacher et al [30] respectively the infection was cleared In the remaining 8 of which one was a case of septic arthritis and the remainder of osteomyelitis [3 1 3] ristocetin exerted a favorable effect in conjunction with surgery Nine of the 11 patients had been treated with antibiotics prior to institution of ristocetin therapy

The following is the case of chronic osteomyelitis reported by Miller et al [1] in which ristocetin affected a cure

A 24 year old Negro man was admitted with osteomyelitis of the right tibia Two years previously he had suffered a compound comminuted fracture of the right tibia and fibula This had been treated by closed reduction and immobilization with a plaster cast and had been followed by open reduction with fixation with an intramedullary nail and a bone graft After removal of the nail another cast had been applied

At the present admission a purulent sinus existed at the side of fracture from which *Staph aureus* and a *Pseudomonas* species were isolated Streptokinase 20 000 units was given buccally every 12 hours for four days Then erythromycin 250 mg was given by mouth every six hours for 18 days During this time a curettage of the right tibia was done Trypsin 5 mg was administered buccally every 12 hours for four days Provided with a molded cuff brace the patient was discharged after a total stay of eight weeks

One month later the patient reinjured his leg, received initial treatment elsewhere and was readmitted with purulent drainage at the original site Penicillin 300 000 units and streptomycin 0 5 Gm were given intramuscularly twice daily for 17 days A small abscess at the site of fracture was incised and drained and a *Staph aureus* was identified Chloramphenicol 250 mg was given by mouth every four hours for 25 days and this was followed by erythromycin, 250 mg by mouth every four hours for 23 days A sequestrectomy was then performed and was followed by concurrent therapy with chloramphenicol 250 mg by mouth every four hours for one month and erythromycin 250 mg by mouth every four hours for six weeks.

Despite this treatment drainage persisted Ristocetin was given at a rate of 1 0 Gm

intravenously every 12 hours for seven days Drainage stopped the wound healed and a walking type plaster cast was applied The patient was discharged 10 days after ristocetin therapy ended The cast was removed one month after his release from the hospital Five months later the wound was still healed and roentgenographic evidence of osteomyelitis was not present

This patient had evident chronic osteomyelitis uninterruptedly for about two and one half years During this period he received excellent treatment along with the administration of antibacterial drugs Healing however was achieved only after treatment with ristocetin This wound had remained healed for five months and the result to date can be considered excellent

Most of the patients with this type of infection were given about 2 Gm of ristocetin per day and in some cases the drug was continued for several weeks without side effects All authors found that the best results were attained when appropriate surgical procedures were combined with ristocetin therapy

In the light of the over all experience with ristocetin the recommended dosage schedule of ristocetin for staphylococcal osteomyelitis and arthritis in adults is 3 Gm /day initially then 2 Gm /day for as long as is necessary From the experience of Terry and Bradley[32] and in view of the gravity of these infections in childhood the initial dosage may be in the range of 50 to 75 mg /Kg /day followed by a dosage of 25 to 50 mg /Kg /day

Staphylococcal Endocarditis [27 33 34] Staphylococci are responsible for approximately 10 to 16 per cent of all cases of endocarditis [1 10] This problem is increasing in importance because of the antibiotic resistant strains of staphylococci that are frequently encountered Therapy has comprised various combinations of antibiotics often including massive dosages of penicillin as high as 30 to 160 million units (18 to 96 Gm)/day [9]

Five of the 7 patients with staphylococcal endocarditis listed in table X were cured with ristocetin therapy while 2 were considered failures All of the patients had been treated with one or several antibiotics before ristocetin was tried and had positive blood cultures when ristocetin was begun Dosage schedules used in the successful cases were as follows Romansky and Holmes[27] used 2 Gm every eight hours Weber[34] administered 1 5 Gm every eight hours and 2 Gm every twelve hours in his 2 cases while Van Rooyen et al[33] used 1 5 Gm every eight hours Dries et al[5] successfully treated an 11 year old girl with 75 mg /Kg /day for 35 days after 25 mg /Kg /day had failed to produce the desired results Each dose of ristocetin was administered in two hours or less The duration of therapy in the 4 adults ranged between 12 and 18 days

The efficacy of ristocetin is illustrated by the following case report [7]

A 25 year old Negro man a heroin addict was admitted to our service with a history of a 30 lb weight loss shortness of breath fever weakness and fatigability The patient s past history revealed no evidence of organic heart disease Physical examination revealed an emaciated *chronically ill man in no acute distress with a blood pressure of*

115 mm systolic and 60 mm diastolic temperature was 106 F pulse 124 and regular A harsh grade III systolic murmur was heard best along the left sternal border as well as at the aortic area Hemoglobin was 10 5 Gm hematocrit 32 volumes/100 ml leukocyte count 12 400/cu mm with 74 per cent polymorphonuclears 20 per cent lymphocytes 5 per cent monocytes and 1 per cent basophils The urinalysis was not remarkable Three blood cultures were positive for coagulase positive hemolytic *Staph aureus* In vitro sensitivity tests revealed that this organism was sensitive to penicillin streptomycin erythromycin chloramphenicol tetracycline and novobiocin It was sensitive to 1 unit/ml ristocetin The intensive preristocetin therapy included penicillin, chloramphenicol erythromycin and novobiocin during a period of 67 days There was no clinical improvement and blood cultures remained positive for coagulase positive hemolytic *Staph aureus* Ristocetin was started on Nov 5 1956 at a dosage of 2 Gm dissolved in 500 ml 5 per cent glucose in water given over a 30 to 60 minute period every eight hours Numerous blood cultures remained negative after initiation of ristocetin therapy and the patient s temperature returned to normal At this dosage level blood concentrations of ristocetin were about 160 units/ml A moderate phlebitis at the site of entrance of the polyethylene tube appeared at the end of therapy and subsequently cleared No other side effects were noted The patient had a good bacteriological and clinical response with a 28 month follow up at the time of this report (February 1959)

The 2 cases of Rantz and Jawetz were classified as treatment failures These patients received 1 5 and 2 0 Gm /day respectively by constant intra venous drip Not only were these daily dosages lower than those given in the successful cases but the method of giving the drug by constant intravenous drip precluded the attainment of peak concentrations During therapy with ristocetin, the serum from their first patient inhibited the organism maximally at a dilution of 1 8 while undiluted serum from patient 2 failed to inhibit growth The failure in these cases may very well be related to a lack of peak concentrations at any time that were sufficient to produce a maximum bac tericidal effect

Staphylococcal endocarditis may require initial dosages of ristocetin on the order of 50 to 75 mg /Kg /day with subsequent reduction to approximately 25 to 50 mg /Kg /day It is particularly important that the infusions be given rapidly

In the successful cases the duration of therapy was 12 to 18 days in 4 cases In the fifth case therapy was continued for 35 days Further clinical experi ence is necessary to define the optimal dosage and duration of therapy

Septicemia [9, 18, 33] The potentially high mortality rate of overwhelming staphylococcal infection of the blood stream demands that therapy be insti tuted promptly

As shown in table X staphylococcal septicemia was the major indication for ristocetin therapy in 8 cases in this series Three patients were cured 2 were improved therapy failed in 2 and 1 patient was successfully treated for two episodes of septicemia one month apart but died of unrelated causes during the second All patients had been treated with other antibiotics prior to ris

tocetin therapy The dosages used were variable Van Rooyen et al[33] had excellent results in 2 cases with 1 to 2 Gm /day while Gangarosa et al[9] used 9 Gm /day in curing the septicemia in their patient with lupus erythematosus The 2 patients showing improvement received 1 to 4 and 3 to 4 Gm /day respectively

Naturally seeking out and eradicating the focus of infection is as important as antibiotic therapy One of the cases reported by Van Rooyen et al[33] is an example of how chemotherapy and surgery can be effectively combined

The patient who was 38 years old and weighed 130 lb was transferred to Camp Hill Hospital on Dec 20 1957 from another institution Here he had been under treatment for diabetes complicated by staphylococcal septicemia with multiple staphylococcal abscesses and arthritis of the right shoulder The patient had a severe brittle diabetes the control of which with superimposed infection presented a difficult combination to manage The accompanying letter from the referring physician stated that, "Every antibiotic possible was used without bringing the temperature to normal" At this stage laboratory investigations revealed the following The hemoglobin level which was maintained by repeated blood transfusions varied between 11 6 and 12 7 Gm /100 ml White cell counts ranged from 9800 to 23 000 Sedimentation rate varied from 18 mm /hour to 43 mm in one hour (Wintrobe and Landsberg method) Urinalysis showed a trace of albumin and a small amount of sugar Bacteriological examination of aspirated pus showed *Proteus vulgaris* and *Staph aureus* as well as *Pseudomonas aeruginosa* and streptococci

Roentgenographic examination of hips knees femurs chest, cervical and dorsal spines and shoulder joints failed to reveal evidence of osseous disease

On December 28 ristocetin was commenced and other antibiotics were discontinued during the next 20 days the patient received a total of 111 Gm of ristocetin Dosage was calculated on the basis of 25 mg /kg body weight. It was made up in 500 ml of 5 per cent dextrose solution and administered intravenously over a period of 45 minutes as recommended The daily dosage ranged from 4 to 1 Gm /day depending on the patient s temperature and general physical condition

Incision and drainage were performed by J A Noble Chief of Surgery Camp Hill Hospital on six occasions On December 27 the right shoulder abscess was opened and 4 ml of pus removed On December 29 an abscess in the left thigh was incised On December 31 the abscess on the right shoulder region was re-explored and drained and on the same date an abscess was located in the left thigh and this was likewise drained From both of these copious pus was liberated On Feb 17 1958 the posteromedial aspect of the right thigh was drained and 500 ml of foul smelling purulent material was obtained On March 11 1958 a fluctuant area in the right costovertebral angle was located and 2200 ml of purulent thin yellow material was released Digital exploration of the abscess cavity revealed a tract extending upward retroperitoneally to behind the lower ribs and thence downward behind the psoas muscles to the iliac crest and fossa

In summary it may be concluded that although several antibiotics other than ristocetin were used at different times for this man the turning point in his illness occurred on March 11 1958 after surgical drainage had been performed and 2 2 liters of pus were evacuated from the psoas region It should be pointed out however that ristocetin was the only antibiotic administered during the critical phase of the illness when massive accumulations of pus were present and septicemia was imminent

The patient of Knight[18] who did not respond received 6 Gm /day the case was complicated by the fact that the patient had been on steroid therapy Knight felt that failure of this patient to respond to several agents effective *in vitro* may have been a measure of impaired host resistance to infection

The patient reported by Rantz and Jawetz did not respond to 4 Gm /day and subsequently died despite intensive chemotherapy with several antibiotics In this instance surgical evacuation of abscesses might have favorably altered the course

The dosage schedules will vary with the severity of the illness but in general initial dosages in the range of 3 to 4 Gm /day (approximately 50 mg /Kg /day) followed by maintenance dosages of 1 to 2 Gm /day (25 to 50 mg /Kg /day) will constitute adequate therapy

Meningitis and Brain Abscess[7 1] Although there have been only 2 reported cases of staphylococcal meningitis treated with ristocetin[7 17] the excellent results obtained in both are encouraging In both instances the patient s condition had deteriorated while he was receiving other antibiotics Kanner s[17] patient was given 1 Gm of ristocetin every six hours while the patient reported by Romansky[7] responded to 2 Gm every eight hours The case reported by Kanner is of particular interest since studies of the spinal fluid showed that ristocetin does cross the blood brain barrier

On Nov 16 1957 at Central Baptist Hospital (Lexington Ky) a 32 year old white woman was delivered under general anesthesia of a healthy child by low forceps Three days later she had a fever (106 F) headache nuchal rigidity and reduced reflexes on the left side with absent plantar reflex Spinal fluid was cloudy and under slightly increased pressure Analysis revealed 711 cells/ml (106 polymorphonuclear leukocytes and 605 lymphocytes) globulin 3 plus and protein 161 mg /100 ml Culture of the fluid produced hemolytic *Staph aureus* coagulase positive as the causative organism By testing with discs the organism was found to be sensitive to the usual antibiotics The tentative diagnosis was septicemia with brain abscess accompanied by secondary meningitis

Treatment consisted of penicillin parenterally and intrathecally erythromycin orally and parenterally and corticoids orally and parenterally However the patient s condition gradually deteriorated and in desperation streptomycin chlortetracycline and sodium sulfadiazine were added to the regimen in full dosage

On the seventh hospital day the patient appeared moribund The hemoglobin had dropped to 8 3 Gm /100 ml necessitating transfusion of whole blood Cortisone was maintained above 200 mg daily On the eighth hospital day Jacksonian type status epilepticus developed requiring large dosages of diphenylhydantoin sodium and phenobarbital sodium Signs of right hemiplegia developed and respiration was Cheyne Stokes a tracheostomy was performed

On the tenth hospital day administration of ristocetin was initiated at a dosage of 1 0 Gm every six hours by intravenous infusion This was accompanied by 15 ml of gamma globulin intramuscularly Multiple trephining was performed in order to drain an accessible brain abscess however the only findings were a thick (1 5 cm) pachymenigitis and a wet brain

On the eleventh hospital day there was marked improvement, which continued steadily except for clinical, roentgenographic and electrocardiographic evidence suggestive of pulmonary embolism on the twelfth day Monilial cystitis developed on the twenty first day but cleared after administration of nystatin orally and vaginally

On the thirty second hospital day all medication was withdrawn The patient's only residua were a silly affect and amnesia for the entire pregnancy Subsequently her personality has returned to normal and parts of her memory loss are clearing.

Ristocetin assays on the spinal fluid of this patient revealed concentrations of 0 32 μg /ml on two occasions when the serum concentration was 0 64 μg /ml On another occasion the spinal fluid concentration was 0 32 μg /ml when the serum concentration was 10 24 μg /ml

A level of 1 25 μg /ml was attained eight hours after a dose on two occasions in the case of Romansky [7] Blood levels at the same time were 40 μg /ml This suggests that while ristocetin may not readily cross uninflamed meninges its diffusion is enhanced in meningitis

The dosage schedule in these patients was 4 to 6 Gm /day There have not been enough patients treated with ristocetin to evaluate dosage schedules The severity of this infection will probably require initial dosages of 50 to 75 mg /Kg /day with subsequent reduction depending on the clinical course

Visceral Infections [7, 32] This category includes a case of staphylococcal enteritis in an infant reported by Terry and Bradley[32] and a patient with

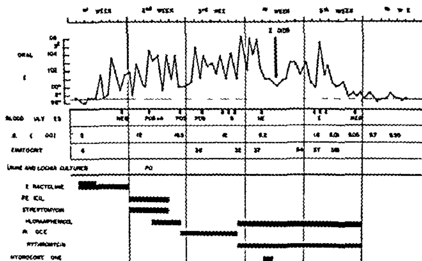


Fig 1 Puerperal endometritis and septicemia (coagulase positive hemolytic *Staph aureus*) in patient L G a 26 year old woman Membranes ruptured prior to delivery Fourth hospital day delivery of stillborn fetus twelfth day chest roentgenogram negative fifteenth day chest roentgenogram showed mottled infiltration in right lung base twenty ninth day hysterectomy

The patient of Knight[18] who did not respond received 6 Gm /day the case was complicated by *the fact that the patient had been on steroid therapy* Knight felt that failure of this patient to respond to several agents effective *in vitro may have been a measure of impaired host resistance to infection*

The patient reported by Rantz and Jawetz did not respond to 4 Gm /day *and subsequently died despite intensive chemotherapy with several antibiotics* In this instance surgical evacuation of abscesses might have favorably altered the course

The dosage schedules will vary with the severity of the illness but in general *initial dosages in the range of 3 to 4 Gm /day (approximately 50* mg /Kg /day) followed by maintenance dosages of 1 to 2 Gm /day (25 to 50 mg /Kg /day) *will constitute adequate therapy*

Meningitis and Brain Abscess [7 1] Although there have been only 2 reported *cases of staphylococcal meningitis treated with ristocetin* [7 17] *the excel*lent results obtained in both are encouraging In both instances the patient s *condition had deteriorated while he was receiving other antibiotics Kanner s*[17] patient was given 1 Gm of ristocetin every six hours while the patient reported by Romansky[7] responded *to 2 Gm every eight hours* The case reported by Kanner is of particular interest since studies of the spinal fluid showed that ristocetin does cross the blood brain barrier

On Nov 16 1957 at Central Baptist Hospital (Lexington Ky) a 32 year old white woman was delivered under general anesthesia of a healthy child by low forceps Three days later she had a fever (106 F) headache nuchal rigidity and reduced reflexes on the left side with absent plantar reflex Spinal fluid was cloudy and under *slightly* increased pressure Analysis revealed 711 cells/ml (106 polymorphonuclear leukocytes and 605 lymphocytes) globulin 3 plus and protein 161 mg /100 ml Culture of the fluid produced hemolytic *Staph aureus* coagulase positive as the causative organism By testing with discs the organism was found to be sensitive to the usual antibiotics The tentative diagnosis was septicemia with brain abscess accompanied by secondary meningitis

Treatment consisted of penicillin parenterally and intrathecally erythromycin orally and parenterally and corticoids orally and parenterally However the patient s condition gradually deteriorated and in desperation streptomycin chlortetracycline and sodium sulfadiazine were added to the regimen in full dosage

On the seventh hospital day the patient appeared moribund The hemoglobin had *dropped to 8 3 Gm /100 ml* necessitating transfusion of whole blood Cortisone was maintained above 200 mg daily On the eighth hospital day jacksonian type status epilepticus developed requiring large dosages of diphenylhydantoin sodium and phenobarbital sodium Signs of right hemiplegia developed and respiration was Cheyne Stokes a tracheostomy was performed

On the tenth hospital day administration of ristocetin was initiated at a dosage of 1 0 Gm every six hours by intravenous infusion This was accompanied by 15 ml of gamma globulin intramuscularly Multiple trephining was performed in order to drain an accessible brain abscess however the only findings were a thick (1 5 cm) pachymeningitis and a wet brain.

bactericidal in concentrations attained by this technique Strains of staphylo cocci resistant to ristocetin have not been reported

The hematological and other side effects such as phlebitis skin eruptions and fever are infrequent with the recommended dosage schedules and mode of administration The dosage of ristocetin is reduced in renal insufficiency since the antibiotic tends to accumulate

ACKNOWLEDGMENT

We gratefully acknowledge the aid of Mrs Arlene M Brown

BIBLIOGRAPHY

1 AFREMOW M L A review of 202 cases of bacterial endocarditis (1948–1952) Illinois M J *107* 67 1955
2 BILLOW B W MARTORELLA F J LUPINI B AND PALEY S S Clinical observa tions on ristocetin a preliminary report on its efficacy and toxicity in 20 unselected severe respiratory infections *In* Antibiotics Annual 1958–1959 New York Medical Encyclopedia Inc 1959 pp 447–453
3 BUSH L F Use of ristocetin (Spontin) in staphylococcal infections *In* Antibiotics Annual 1958–1959 New York Medical Encyclopedia Inc 1959 pp 454–457
4 COHN I AND LONGACRE A B Ristocetin and ristocetin neomycin for preoperative preparation of the colon A M A Arch Surg *77* 224 1958
5 DRIES C P ASAY L D AND KOCH R Ristocetin serum levels in children *In* Antibiotics Annual 1958–1959 New York Medical Encyclopedia Inc 1959 pp 4 8–431
6 EISENBERG W AND KIRSCHBAUM A Turbidimetric method for ristocetin personal communication Antibiotic Division U S Food and Drug Administration
7 ROMANSKY M J (panel discussion) The current status of erythromycin kanamy cin novobiocin oleandomycin ristocetin and vancomycin with particular reference to their use in staphylococcal disease *In* Antibiotics Annual 1958–1959 New York, Medical Encyclopedia Inc 1959 pp 1051–1072
8 FISHER M W AND MANNING M C The specific antibody nature of the thera peutic action of gamma globulin in experimental bacterial infections in mice *In* Antibiotics Annual 1957–1958 New York Medical Encyclopedia Inc 1958 pp 572–576
9 GANGAROSA, E J LANDERMAN N S ROSCH P J AND HERNDON E G JR. Hematologic complications arising during ristocetin therapy relation between dose and toxicity New England J Med *259* 156 1958
10 GERACI J E The antibiotic therapy of bacterial endocarditis M Clin North America p 1101 July 1958
11 GRUNDY W E ALFORD E F RDZOK E J AND SYLVESTER J C Ristocetin the development of resistance and bactericidal activity *In* Antibiotics Annual 1956–1957 New York Medical Encyclopedia Inc 1957 pp 693–698
12 GRUNDY W E. HOLPER J C ALFORD E. F RICKHER C J VOJTKO C M AND SYLVESTER J C Ristocetin a microbiological comparison of ristocetins A and B *In* Antibiotics Annual 1957–1958 New York, Medical Encyclopedia, Inc 1958 pp 158–162
13 GRUNDY W E SINCLAIR, A C THERIAULT R J GOLDSTEIN A W RICKHER C J WARREN H B JR OLIVER T J AND SYLVESTER J C Ristocetin micro-biologic properties *In* Antibiotics Annual 1956–1957 New York Medical Encyclo pedia Inc 1957 pp 687–692
14 HOLPER J C RICKHER, C J AND SYLVESTER J C Ristocetin effect of gamma globulin on in vivo activity *In* Antibiotics Annual 1957–1958 New York, Medical Encyclopedia Inc 1958 pp 577–580

puerperal endometritis reported by Romansky[7] Both patients were critically ill and had been treated with other antibiotics before ristocetin was started

The infant recovered in three days when given 150 mg/day intravenously In the case reported by Romansky ristocetin successfully cleared bacteremia that had been refractory to other antibiotics but the patient remained febrile until a necrotic uterus was removed

A 26 year old Negro woman was admitted to the hospital in labor and several hours later the membranes ruptured (fig 1) Labor continued for 2½ days at which time a stillborn fetus was delivered The patient was given tetracycline prophylactically during labor but after delivery she developed fever and foul smelling lochia was noted On the seventh hospital day therapy was changed to penicillin and streptomycin and later chloramphenicol was added Despite this she continued to have a septic fever developed a mottled infiltrate in the right lung base and progressively deteriorated Cultures of blood and lochia obtained during combined therapy yielded an abundant growth of coagulase positive hemolytic *Staph aureus* This organism was sensitive in vitro to chloramphenicol erythromycin ristocetin and novobiocin On the fourteenth hospital day all medication was stopped and ristocetin was begun at a dosage of 3 Gm every eight hours After the second day of ristocetin therapy negative blood cultures were obtained but the patient continued to have a septic fever and was very toxic Ristocetin was discontinued after one week and chloramphenicol and erythromycin were given along with intravenous hydrocortisone The steroid temporarily brought the temperature down and improved the general condition By the twenty-eighth hospital day the patient s condition had again deteriorated and pelvic exploratory laparotomy was elected A grossly necrotic uterus was found and removed After surgery her temperature became normal and convalescence was uneventful No side effects of ristocetin were noted

It is evident that although ristocetin therapy eliminated the sepsis and contained the infection cure was attained only when a necrotic focus the uterus was removed In retrospect the continued fever was a reflection of this necrotic focus and earlier surgery rather than continued chemotherapy was indicated

In summary 89 cases representing a variety of staphylococcal infections treated with ristocetin were found in the literature Fifty seven patients or 63 9 per cent were cured while an additional 19 or 21 3 per cent showed improvement There were 6 failures (6 7 per cent) and 7 (7 8 per cent) patients died of unrelated causes or before ristocetin could be evaluated Dosage schedules varied with the type and severity of infection but generally ranged between 25 and 50 mg/Kg/day Focal suppuration is characteristic of staphylococcal infections and appropriate surgical measures should be employed with chemotherapy

CONCLUSIONS

Ristocetin is an effective primary agent in staphylococcal infections as well as in short term therapy of enterococcal endocarditis It is administered intravenously intermittent rapid infusion is recommended Ristocetin is

Chapter VII | Kanamycin

Ellard M Yow
Department of Medicine Baylor University College of Medicine
and the Ben Taub Infectious Disease Laboratory
Jefferson Davis Hospital Houston Texas

Kanamycin was isolated from *Streptomyces kanamycetus* by Umezawa [6, 27] at the Japanese National Institute of Health and Tokyo University in 1957 The original material contained two fractions A and B but the presently manufactured antibiotic is almost pure kanamycin A The initial in vitro and in vivo studies in Japan demonstrated that kanamycin was active against many gram negative pathogens against strains of staphylococci resistant to other antibiotics and against streptomycin and isoniazid resistant strains of *Mycobacterium tuberculosis* Clinical studies were carried out initially on cases of pulmonary tuberculosis but subsequent clinical reports showed the drug to be effective against infections due to a wide range of microorganisms At a recent conference on kanamycin held at the New York Academy of Sciences in July 1958 the pharmacological studies and clinical experiences on the use of the drug to date were presented [1]

CHEMISTRY

Cron and his co workers[7] determined the chemical composition of kanamycin and showed that hydrolysis will yield two amino sugars linked glycosidically to 2 dioxystreptamine The drug is water soluble and stable through a *p*H range of from 2 to 11 under normal sterilizing conditions and at a boiling temperature for 30 minutes at a *p*H of 6 to 8 The structural formula resembles that of *neomycin in that there is a common dioxystreptamine moiety but* the two antibiotics differ in the amino sugars (see fig 1)

15 HSIE, J Y NUSSER W EPSTEIN S., VAN MAREN H AND OZOG S Staphylococcal resistance to ristocetin oleandomycin and novobiocin Antib & Chemo 8 607-614 1958
16 HWANG K PRIMACK, N STEIN R J AND RICHARDS R K Pharmacological and toxicological properties of ristocetins A and B In Antibiotics Annual 1957-1958 New York, Medical Encyclopedia Inc 1958 pp 163-179
17 KANNER I F Ristocetin in the cerebrospinal fluid during staphylococcal meningitis. In Antibiotics Annual 1958-1959 New York Medical Encyclopedia, Inc 1959 pp 432-436
18 KNIGHT V The staphylococcal problem today J Kentucky M 56 1110 1958
19 LOO Y H SHELL, P S THORNBERRY H H, EHRLICH J MCGUIRE J M SAVAGE G M AND SYLVESTER J C Assay of streptomycin by the paper-disc plate method, J Bact 50 701 1945
20 MELTON J T AND LOGUE B Treatment of staphylococcal endocarditis A M A Arch Int Med 99 581 1957
21 MILLER J M GINSBERG M BARANOWSKI J A AND MCELFATRICK, G C Ristocetin in the treatment of seven selected difficult cases In Antibiotics Annual 1958-1959 New York Medical Encyclopedia Inc 1959 pp 441-446
22 NEWTON R M AND WARD V G Leukopenia associated with ristocetin (Spontin) administration report of two cases J A M A 166 1956-1959 1958
23 PHILIP J E SCHENCK J R AND HARGIE M P Ristocetins A and B two new antibiotics isolation and properties In Antibiotics Annual 1956-1957 New York Medical Encyclopedia Inc 1957 pp 699-705
24 RAMMELKAMP C H A method for determining the concentration of penicillin in body fluids and exudates Proc Soc Exper Biol & Med 51 950 1942
25 RANTZ L A AND JAWETZ, E Failure of ristocetin therapy in three cases of staphylococcal sepsis with bacteremia, New England J Med 259 963 1958
26 ROMANSKY M J Unpublished data
27 ROMANSKY M J AND HOLMES J R Successful short term therapy of enterococcal and staphylococcal endocarditis with ristocetin—seven patients In Antibiotics Annual 1957-1958 New York Medical Encyclopedia Inc 1958 pp 187-198
28 ROMANSKY M J LIMSON B M AND HAWKINS J E Ristocetin a new antibiotic —laboratory and clinical studies Preliminary report In Antibiotics Annual 1956-1957 New York Medical Encyclopedia Inc 1957 pp 706-715
29 SCHNEIERSON S S AMSTERDAM D AND BRYER, M S Bacterial sensitivity to ristocetin Antib & Chemo 8 204-207 1958
30 SCHUMACHER L R SOWELL R C COATES J R AND CALVY G L Experience with ristocetin in staphylococcal pneumonia observations in 24 patients In Antibiotics Annual 1958-1959 New York Medical Encyclopedia Inc 1959 pp 464-471
31 SHIDLOVSKY B A AND PRIGOT A The influence of combinations of ristocetin and neomycin on intestinal aerobic microflora In Antibiotics Annual 1958-1959 New York Medical Encyclopedia Inc 1959 pp 770-773
32 TERRY R B AND BRADLEY L F Ristocetin in adults and children In Antibiotics Annual 1958-1959 New York Medical Encyclopedia Inc 1959 pp 458-463
33 VAN ROOYEN C E MACLEOD A J AND EMBREE, G Ristocetin a clinical trial Canad M A J 79 723 1958
34 WEBER R W Staphylococcic endocarditis treated with ristocetin J A M A 168 1346-1351 1958

TABLE I

Sensitivity of Various Microorganisms to Kanamycin In Vitro

Organisms usually sensitive	Organisms occasionally sensitive	Organisms usually resistant
Staphylococci	*Proteus*	Pneumococcus
E coli	*Pseudomonas*	*Streptococcus*
Aerobacter Klebsiella		Yeast
B anthracis		Fungi
Neisseria gonorrhoeae		Anaerobic microorganisms
Salmonella		(anaerobic streptococci
Shigella		clostridia and *bacteroides*)
Brucella		

produced by subacute or chronic administration of kanamycin was evident on the vestibular and auditory functions of the experimentally treated animals similar to that produced by streptomycin and dihydrostreptomycin although much larger dosages and longer periods of administration were required to produce similar effects [5] Dogs were given kanamycin intramuscularly in dosages as large as 100 mg /Kg /day for nine months without evidence of toxicity Cats receiving the same dosage and dogs receiving 200 mg /Kg /day developed vestibular disturbances in two to four weeks but not to the same extent as animals receiving the same dosage of streptomycin sulfate When dogs were given daily intramuscular injections of 200 mg /Kg of kanamycin sulfate there was evidence of kidney damage as manifested by albuminuria hematuria decreased phenolsulfonphthalein excretions increased blood urea nitrogen and if continued sufficiently long anuria At dosages of 200 mg /Kg two to three weeks were required for definite signs of damage but at dosages of 380 mg /Kg these signs appeared rapidly Post mortem examination of the dogs dying during these toxicological studies showed microscopic evidence of cloudy swelling of the proximal tubule to acute necrosis of the proximal and distal tubules in the animals showing anuria Neomycin produced renal toxicity in dogs in dosages as low as 24 mg /Kg /day intramuscularly after one month of treatment and when the dosage was increased to 96 mg /Kg /day dogs died within one to three weeks [15] Studies of auditory toxicity in rats suggest that kanamycin is less toxic than dihydrostreptomycin [5]

ANTIBACTERIAL ACTIVITY IN VITRO

Microbiological studies on kanamycin have revealed a wide spectrum of in vitro activity against staphylococci the *Bacillus* group *Vibrio Salmonella Shigella* mycobacteria and some strains of *Proteus* and *Pseudomonas* The antibiotic is relatively inactive against most streptococci pneumococci and most anaerobic organisms [14] (See table I) The antibacterial action of kana

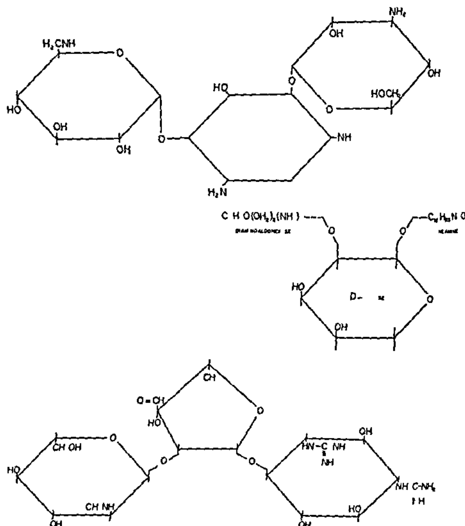


Fig 1 Structural formulas of k namycin (top) neomycin (middle) and streptomycin (bottom)

ANIMAL TOXICITY

Toxicity studies on laboratory animals have shown the acute toxicity to be somewhat less than that of streptomycin the LD$_{0}$ of streptomycin in mice being 200 mg/Kg by the intravenous route and 900 mg/Kg by the subcutaneous route as compared with kanamycin sulfate with an intravenous LD$_{0}$ of 316 to 1648 mg/Kg when injected subcutaneously [5] The approximate LD$_{50}$ of neomycin by the subcutaneous route is 250 mg/Kg which is about one fifth the toxicity of the intravenously administered drug [13] Toxicity

the type of media being used and to a lesser extent the duration of the incubation Utilizing the tube dilution technique as performed by Gourevitch et al[13] in which heart infusion broth is used and the inoculum is a 1 10 000 dilution of an overnight broth culture all staphylococci are inhibited by concentrations of 6 25 μg /ml or less[14, 33] Similar results were obtained by the use of Trypticase soy broth[9] If the agar streak method is used concentrations required to inhibit most microorganisms are approximately two to four times as great as with the tube dilution test just described[19] This difference approximates that previously described in studies with other antibiotics If brain heart infusion broth is used rather than heart infusion broth in the serial dilution technique the inhibitory concentration is approximately three to four times as great and if the size of the inoculum is increased to 10^{-2} from 10^{-4} dilution of an overnight culture the concentration of kanamycin required to produce bacteriostasis is two to four times greater[16] Certain additions to the culture media such as phosphates or chlorides have been shown to protect bacterial cells from the action of kanamycin[14] The nature of this protection is not known

Kanamycin is active in vitro against *Myco tuberculosis* in a concentration of 2 5 μg /ml in polysorbate 80 albumin medium and 10 μg /ml in Proskauer and Beck s medium plus 10 per cent horse serum[23]

Kanamycin exhibits complete cross resistance with neomycin that is all neomycin resistant strains of organisms are kanamycin resistant and neomycin sensitive strains are kanamycin sensitive

There are quantitative differences between the susceptibility of various microorganisms to kanamycin and neomycin neomycin generally being slightly more actively bacteriostatic on a weight basis[16, 9, 33] The reverse appears to be true of the bactericidal effect[9] Gourevitch and co workers[14]

TABLE II

to Kanamycin and Other Antibiotics

Erythro mycin	Chloram phenicol	Baci tracin	Novo biocin	Poly myxin	Vanco-mycin	Risto cetin
60	82	91	97	0	100	100
40	18	9	3	100	0	0
0	57	0	0	77	0	0
100	43	100	100	23	100	100
0	35	0	17	23	0	0
100	65	100	83	77	100	100

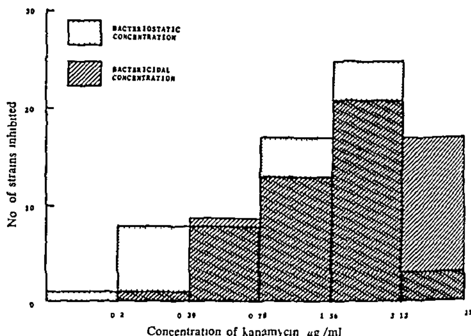


Fig 2 Concentration of kanamycin (μg /ml) required to inhibit 62 strains of staphylococci (Reprinted with permission from Yow and Monzon [33])

mycin is primarily bactericidal in that the bactericidal concentration of the antibiotic is approximately equal to the concentration required to produce bacteriostasis[33] (see fig 2)

The precise concentration of kanamycin required to inhibit various microorganisms in vitro varies depending on the size of the inoculum being tested

TABLE II

Comparative Sensitivity of Various Organisms

Organisms studied	Kanamycin	Neomycin	Penicillin	Streptomycin	Tetracycline
Staphylococci (91 strains)					
% sensitive	100	100	35	35	38
% resistant	0	0	65	65	62
Coli-aerogenes group (21 strains)					
% sensitive	100	100	0	47	57
% resistant	0	0	100	53	43
Proteus Pseudomonas group (17 strains)					
% sensitive	83	83	5	47	35
% resistant	17	17	95	53	65

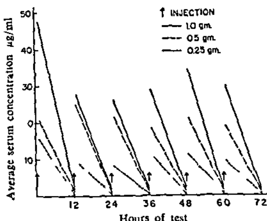


FIG. 5 Average serum concentrations 1 and 12 hours after repeated injections of kanamycin at three dosage levels 0.25 0.5 and 1.0 Gm Ten subjects were used at each dosage level (Reprinted with permission from Welch et al[2])

and little drug can be detected in the serum 12 hours after a single injection The levels attained in the serum are approximately the same as those after an equivalent dose of streptomycin or dihydrostreptomycin[9] (see fig 3) Most of the antibiotic is excreted in the urine within 24 hours after it is administered approximately 80 per cent being excreted in the first six hours after medication[9] (see fig 4) There is no accumulation of kanamycin in the serum when given at 12 hour intervals (see fig 5) There is little serum binding of the antibiotic[9] Kanamycin is excreted exclusively by glomerular filtration after parenteral administration[25]

Kanamycin is distributed in highly vascular organs such as the liver and kidney and appears in concentrations approximately equivalent to the blood level Penetration into the spinal fluid bone and heart muscle is quite poor[5]

There has been little experience with the intravenous administration of kanamycin since it is absorbed so rapidly after intramuscular injection Apparently the antibiotic is tolerated well when administered intravenously in that thrombophlebitis does not seem to be a problem

Kanamycin is so poorly absorbed after oral administration (4.0 Gm./day) that blood levels are extremely low or not detectable[4]

THE TREATMENT OF INFECTIONS EXPERIMENTALLY PRODUCED IN ANIMALS

Acute infections produced by the intraperitoneal injection of mouse virulent and kanamycin sensitive strains of *Diplococcus pneumoniae Klebsiella pneumoniae Proteus vulgaris* and *Staph aureus* respond to kanamycin in a fashion similar to that seen after the administration of penicillin streptomycin tetracycline erythromycin and chloramphenicol but mice infected with a

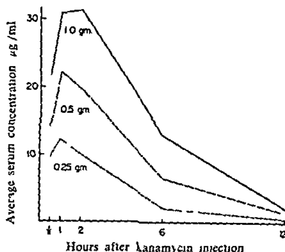


FIG 3 Average serum concentrations after single intramuscular injections of kanamycin at three dosage levels 0 25 0 5 and 1 0 Gm Ten subjects were used at each dosage level (Reprinted with permission from Welch et al [29])

using serial transfer techniques on *Staphylococcus aureus* and *Escherichia coli* have demonstrated the development of resistance to kanamycin in vitro in a slow, stepwise fashion Resistance of mycobacteria develops at a more rapid rate Such resulting resistant strains follow the pattern of complete cross resistance to neomycin and incomplete cross resistance to viomycin Umezawa [6] reported that a strain of *E coli* made resistant to kanamycin also developed resistance to streptomycin However a similar relationship was not found with mycobacteria No cross resistance to kanamycin with any of the other antibiotics has been consistently demonstrated in our laboratories (see table II)

ABSORPTION DISTRIBUTION AND EXCRETION

Kanamycin is absorbed rapidly when injected intramuscularly peak concentrations being reached within one hour The levels fall rapidly within six hours

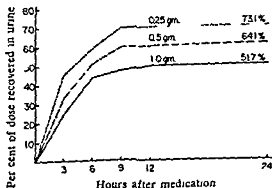


FIG 4 Cumulative percentage of kanamycin dose recovered in the urine after single intramuscular injections of 0 25 0 5 and 1 0 Gm Each curve represents the composite results from 10 subjects (Reprinted with permission from Welch et al [2])

TABLE III

Responses of Various Infections to Kanamycin

Infections that have responded favorably to kanamycin	Infections that have not usually responded to kanamycin
Staphylococcal infections	Pneumococcal infections
Furunculosis Septicemia Endocarditis Osteomyelitis	Streptococcal infections Typhoid fever *Brucellosis*
Infections due to *E coli*	Most cases of infection due to *Pseudomonas*
Wound infections Urinary tract infections	Some cases of *Proteus* infections
Infections due to *Aerobacter Klebsiella*	Infections caused by yeast fungi, and anaerobic organisms
Urinary tract infection Wound infections Pneumonias	
Most cases of *Proteus* infections	
Anthrax *Salmonellosis* Shigellosis	

or more a week and 59 received less than 4 Gm a week Streptomycin was administered twice a week in 1 Gm doses All patients were given 10 Gm of para aminosalicylic acid daily One of the patients had disseminated disease but none had meningitis It was concluded by this group that kanamycin–para aminosalicylic acid has a therapeutic effect almost equivalent to that of streptomycin–para aminosalicylic acid Kanamycin was effective in treating patients with infections due to organisms resistant to one or more combinations of streptomycin isonicotinic acid hydrazide and para aminosalicylic acid No kanamycin resistant strains of tubercle bacilli appeared during therapy in this study but they have been isolated from patients treated with kanamycin in another study[31]

The effect of the oral administration of kanamycin on the bacterial flora of the intestinal tract appears to be identical with that of neomycin that is the coliform bacteria *Proteus Pseudomonas* and *Klebsiella* are usually rapidly eliminated but the fecal streptococci *Monilia Bacteroides* and clostridia usually persist[5, 6] This suppressive effect of kanamycin and neomycin on the bacterial flora of the bowels is presumably the explanation for the lowering of the blood ammonia associated with the administration of either in patients with liver failure[5] Some patients required dosages as large as 8 to 12 Gm daily to produce a reduction and in some the effect was not sustained or reproducible[10]

kanamycin resistant strain of *Streptococcus hemolyticus* were not protected by kanamycin therapy [18] Kanamycin protected against death and reduced the number of viable organisms when administered to mice with long term staphylococcal infection [18] Tests carried out using an overwhelming intravenous challenge of staphylococci resistant to penicillin streptomycin tetracycline and erythromycin showed that kanamycin was effective where the other antibiotics were not [18]

In the treatment of guinea pigs infected with tubercle bacilli, kanamycin appears to be less active than isonicotinic acid hydrazide and slightly less effective than streptomycin [3] but more active than para aminosalicylic acid Kanamycin produced beneficial effects in animals infected with strains resistant to streptomycin para aminosalicylic acid and isonicotinic acid hydrazide [82]

CLINICAL USES OF KANAMYCIN

Kanamycin has been used in the treatment of a wide variety of bacterial infections and the clinical results have generally paralleled the in vitro studies Most acute infections due to such kanamycin sensitive organisms as *Staph aureus E coli Myco tuberculosis Bacillus anthracis* and the *Aerobacter Klebsiella* group have responded quite promptly to the administration of kanamycin Infections due to sensitive strains of *Proteus* and *Pseudomonas* have likewise improved Infections due to species generally resistant such as *D pneumoniae* most streptococcal species and most anaerobic organisms or to resistant strains of *Proteus Pseudomonas* and the *Aerobacter Klebsiella* group have not been favorably influenced by kanamycin therapy (See table III)

Some very striking exceptions occur in this in vitro–in vivo relationship although *Brucella* and *Salmonella* for example are quite sensitive in vitro to kanamycin patients with brucellosis and typhoid fever treated with kanamycin have not usually responded clinically [1] The course of some other *Salmonella* infections and most *Shigella* infections treated thus far has been altered favorably by kanamycin therapy [4]

The use of kanamycin in the treatment of various forms of tuberculosis has thus far been most extensive in patients failing to respond to established forms of therapy but results have generally been quite encouraging [3 31] Beginning in September 1957 the Japanese Committee on Chemotherapy for Tuberculosis undertook to make a comparative evaluation of kanamycin in the treatment of this disease [8] A report one year later included 110 patients who had received kanamycin for more than two months Fifty two patients with similar backgrounds were treated with streptomycin The routine kanamycin dosage schedule utilized was 1 or 2 Gm a day twice a week though larger dosages were given in the early part of the study so that 51 patients received 4 Gm

otitis media meningitis brain abscesses acute endocarditis acute osteomyelitis *pyelonephritis wound infections furunculosis suppurative thrombophlebitis* empyema prostatic abscesses and infected gangrene [4, 11, 0, 30, 33, 34] Most of the patients treated had already failed to respond to one or more other antibiotics and many of the patients had other serious systemic diseases (see figs 6 to 9)

Since the administration of kanamycin favorably alters the course of most staphylococcal infections its limitations can best be understood by a more detailed study of the reports of its failures One of the most frequent causes of failure seen in association with the evaluation of any new antibiotic today is the presence of far advanced disease interfering with the function of one or more organ systems necessary to maintain life In some instances failure has been due to damage produced by the infectious process and in others infections simply complicated some other irreversible degenerative or neoplastic disorders This situation is inevitable today in that the clinical investigator is not justified in treating diseases known to respond to other antibiotic agents at least not without a clinical trial with several such agents prior to the administration of a new and unevaluated agent As experience with kanamycin increased and its advantages and disadvantages were better understood patients were treated earlier and more adequately and fewer failures occurred for this reason (figs 10 and 11)



FIG 7 Carbuncles in a diabetic which promptly disappeared after kanamycin treatment

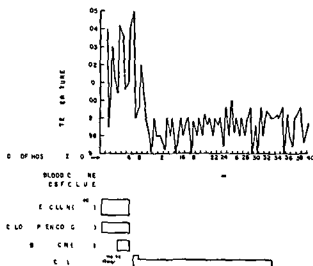


FIG 6 Staphylococcal septicemia and pneumonia in a 1 year old girl

Kanamycin has been used locally in the treatment of superficial infections and as a supplement to its systemic administration Ointments containing 0 5 to 3 mg /ml produce an effect similar to that associated with the use of neomycin in superficial pyodermas Because of the difficulties associated with the sterilization of walled-off infections and infections in body cavities with systemically administered antibiotics kanamycin has been instilled locally in abscess cavities draining sinuses the peritoneal cavity pleural spaces and subarachnoid space The concentration injected into the subarachnoid space has been 0 5 mg /ml and the largest daily dosage has been 5 mg Concentrations varying from 2 5 to 50 mg /ml have been used in other sites with a maximum daily dosage of 1 0 Gm [33] It is highly likely that at least part of the antibiotic instilled locally is absorbed so that this must be taken into consideration in calculating the total daily dosage to be given the patient

THE USE OF KANAMYCIN IN STAPHYLOCOCCAL INFECTIONS

Even though there are quantitative variations in the sensitivity of staphylococci to kanamycin in vitro depending on the method used all strains studied thus far appear to be inhibited in vivo when the presently recommended dosages are used and if the antibiotic actually comes in contact with the bacteria The single exception to this occurs in some instances of so called overwhelming infections as is seen in acute staphylococcal endocarditis

Examples of the beneficial and sometimes lifesaving effect of kanamycin in the treatment of many staphylococcal infections have now been reported These include such conditions as pneumonia lung abscesses acute sinusitis

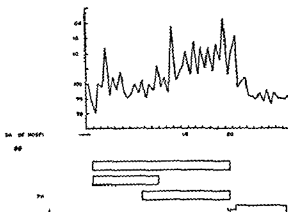


FIG. 9 Appendicial abscess in a 12 year old boy due to *Staphylococcus* with prompt response to kanamycin therapy

Another limitation to the effectiveness of kanamycin (and of all antibiotics for that matter) is its inability to eradicate staphylococci harbored in areas without an adequate vascular supply The most likely explanation for this failure is that the antibiotic is unable to reach the causative organism when administered systemically such as in areas of necrosis fibrosis and in non viable tissues or foreign bodies Another possible explanation is that these same circumstances are often not favorable for growth of bacteria and they survive as nonmetabolizing persisters This limitation has been seen clinically when efforts were made to treat such infections as undrained abscesses chronic *osteomyelitis chronic empyema infected prostheses and infected gangrene* due primarily to arterial insufficiency In most instances kanamycin controlled the bacteremia associated with these conditions and suppressed the cellulitis surrounding the localized infection The local instillation of the antibiotic such as in the pleural or subarachnoid spaces effectively supplemented the systemic administration of the drug but usually surgical drainage or removal of foreign bodies was required to produce more than a transient suppression of the infection

The activity of all antibiotics is influenced in vitro by the number of organisms per milliliter of the inoculum being tested It is likely that under extreme circumstances a very heavy bacterial count may be a cause of failure in certain clinical conditions At any rate this seems to be the explanation for the failure of most antibiotics to control the blood stream infection due to organisms *susceptible in vitro when the colony count is extremely high* This may be seen clinically in severe septicemia and classically in acute bacterial endocarditis secondary to severe septicemia Some patients with staphylococcal septicemia even those with acute endocarditis have responded to kanamycin therapy after failing to respond to other antibiotics active in vitro against the

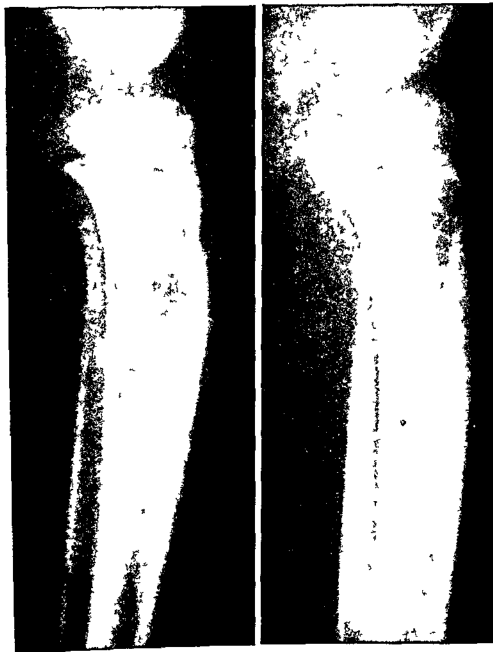


FIG 8 Osteomyelitis of the tibia of two years duration treated with surgery and kanamycin injections (90 days) *Left* Roentgenogram of tibia before treatment *Right* Roentgenogram of tibia after treatment was completed

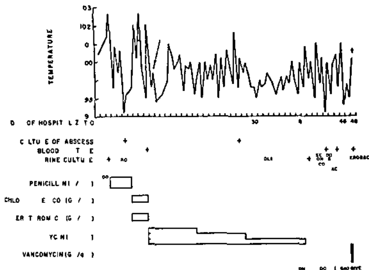


FIG 11 Staphylococcal thrombophlebitis cellulitis and septicemia in a 52 year old diabetic man Kanamycin failed to cure this patient permanently

ammonia intoxication due to liver failure and it might well be used for the treatment of such enteric infections as staphylococcal enterocolitis Kanamycin has been administered intravenously in a few cases but this route offers little advantage since the antibiotic is absorbed so rapidly when injected intramuscularly The tolerance of kanamycin administered by the intravenous route has not yet been adequately evaluated Kanamycin can be administered locally and concentrations of 2 5 mg /ml have not appeared to be irritating to serous or mucous membranes Concentrations of 5 mg /ml or more have been instilled into abscess cavities without pain or other evidence of irritation

Optimum safe dosages of kanamycin for the treatment of tuberculosis have not been established but 1 0 Gm given twice weekly seems to be adequate Another antimicrobial antibiotic should be administered along with kanamycin in order to decrease the frequency and rate of the appearance of resistant forms

The presently recommended dosages of kanamycin are summarized in table IV No more than 40 Gm should be given in a single course of therapy under most circumstances and in elderly patients and patients with poor renal function the total dosages should be further limited

TOLERANCE UNTOWARD SIDE EFFECTS AND TOXICITY

The pain associated with the intramuscular injection of kanamycin has



FIG 10 Staphylococcal septicemia and septic thrombophlebitis that failed to respond Same patient as Fig 11

causative organism There have been failures in this group however In sub acute staphylococcal bacterial endocarditis where the pathological process is similar in most respects but the number of circulating bacteria is much smaller therapy with kanamycin has been successful when the causative agent was kanamycin sensitive

A final problem associated with the treatment of staphylococcal infections has been the tendency of kanamycin resistant species to take over the infec tious process after the staphylococci have been eliminated This is most likely to occur in chronic infections of mixed etiology or infections exposed to a contaminated environment such as empyema with a bronchopleural fistula infected burn lung abscess and infection of the skin and subcutaneous tissues

ADMINISTRATION AND DOSAGE

Kanamycin is usually administered by the intramuscular route in systemic infections The drug is not sufficiently absorbed when administered by the oral route to produce therapeutic levels but this method of administration has been used as a means of preparing the patient for bowel surgery and for treating

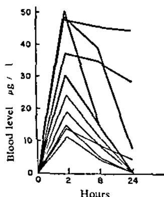


FIG 12 A comparison of blood levels of kanamycin in patients with normal and elevated serum creatinine after intramuscular injection of 1 Gm kanamycin Thick line indicates creatinine greater than 3 mg /100 ml Thin line indicates serum creatinine less than 3 mg /100 ml

much longer periods of therapy were required to produce audiographic changes In most instances the hearing loss begins in the high frequency ranges and is preceded by tinnitus If the antibiotic is discontinued during the period that tinnitus is prominent withdrawal of the drug results in a prevention of the hearing loss If kanamycin is continued permanent loss progresses as long as the drug is given but not after it is discontinued

Observations by several investigators[17 33 34] suggest that children tolerate larger amounts of kanamycin One 6 year old child for example received dosages from 30 to 60 mg /Kg /day for 40 days without audiographic evidence of hearing loss and another received between 35 and 50 mg /Kg /day for 90 days

A factor of considerable importance in regard to auditory toxicity appears to be the rate at which the antibiotic is excreted Since kanamycin is excreted almost exclusively by glomerular filtration disorders associated with a decreased glomerular filtration are likely also to be associated with increased blood levels of kanamycin (fig 12) and consequent increased toxicity This is most likely to be observed in diabetic patients with insufficiently severe Kimmelstiel Wilson s disease to produce an elevated creatinine Two of the 3 patients developing severe hearing loss in Houston had Kimmelstiel Wilson s disease [3] Hearing loss has been reported to occur as early as one week after beginning therapy in patients with marked renal insufficiency [11 8]

Another problem regarding the toxicity of kanamycin in patients is that of renal injury Experience with the use of the closely related antibiotic neomycin and the results of animal toxicity experiments with kanamycin strongly suggested that this would be a problem in the clinical use of the antibiotic While many patients receiving kanamycin exhibit evidence of mild renal irritation as manifested by cylindruria and occasionally albuminuria and microscopic hematuria the only clear-cut evidence of serious renal toxicity was

TABLE IV

Dosage Recommendations for Kanamycin

Intramuscular	Oral	Local
Adults		
1 Gm every 8 hours in severe illness	4 to 8 Gm daily (for sterilization of bowel)	2 5-5 mg /ml
0 5 Gm every 6 hours in moderately severe illness		
0 5 Gm every 8 or 12 hours in mild illness		
Children		
50 mg /Kg body weight per day in severe illness		
25 mg /Kg body weight per day in moderately severe illness		
12 5 mg /Kg body weight per day in mild illness		

about the same severity as that associated with the administration of similar amounts of streptomycin or neomycin If the antibiotic is injected deep in gluteal muscles in the upper and outer quadrant of the buttocks just below the iliac crest and well above and lateral to the sciatic notch pain is rarely a significant problem

Experience with the intravenous administration of kanamycin has been limited but if 1 Gm is given in 500 ml of physiological saline or 5 per cent glucose in water *there is no significant vascular inflammation produced*

Kanamycin is well tolerated when administered orally but an increase in the number of stools may be encountered similar to that associated with neomycin therapy

The greatest hazard of kanamycin therapy is injury to the acoustic nerve This is similar to that seen in association with the administration of dihydro *streptomycin and neomycin Animal toxicity studies indicate that this is* related to the daily dosage and the total amount administered

It has been difficult to appraise accurately the details of the toxic effect of kanamycin on the eighth cranial nerve because of the seriousness of the illness of most of the patients receiving kanamycin and the variations in the dosage schedules in the early months of its clinical trials but the most careful studies *have been performed by Finegold et al* [11] *The findings of this group indicated* that if frequent audiograms are performed perceptive hearing loss of 40 decibels or less can be demonstrated not infrequently in patients receiving greater than 40 mg /Kg /day for periods of more than two weeks Of 11 patients receiving dosages of from 40 to 60 mg /Kg /day for 6 to 28 days 9 showed audiographic changes and 3 of the 9 had losses in the conversational range *Three of the 11 also had evidence of vestibular damage Five of these* patients had pre-existing renal damage In patients receiving smaller daily dosages much milder and often transient auditory damage was evident and

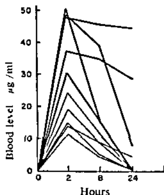


FIG 12 A comparison of blood levels of kanamycin in patients with normal and elevated serum creatinine after intramuscular injection of 1 Gm kanamycin Thick line indicates creatinine greater than 3 mg/100 ml Thin line indicates serum creatinine less than 3 mg/100 ml

much longer periods of therapy were required to produce audiographic changes In most instances the hearing loss begins in the high frequency ranges and is preceded by tinnitus If the antibiotic is discontinued during the period that tinnitus is prominent withdrawal of the drug results in a prevention of the hearing loss If kanamycin is continued permanent loss progresses as long as the drug is given but not after it is discontinued

Observations by several investigators[17 33 34] suggest that children tolerate larger amounts of kanamycin One 6 year old child for example received dosages from 30 to 60 mg/Kg/day for 40 days without audiographic evidence of hearing loss and another received between 35 and 50 mg/Kg/day for 90 days

A factor of considerable importance in regard to auditory toxicity appears to be the rate at which the antibiotic is excreted Since kanamycin is excreted almost exclusively by glomerular filtration disorders associated with a decreased glomerular filtration are likely also to be associated with increased blood levels of kanamycin (fig 12) and consequent increased toxicity This is most likely to be observed in diabetic patients with insufficiently severe Kimmelstiel Wilson s disease to produce an elevated creatinine Two of the 3 patients developing severe hearing loss in Houston had Kimmelstiel Wilson s disease[33] Hearing loss has been reported to occur as early as one week after beginning therapy in patients with marked renal insufficiency[11 8]

Another problem regarding the toxicity of kanamycin in patients is that of renal injury Experience with the use of the closely related antibiotic neomycin and the results of animal toxicity experiments with kanamycin strongly suggested that this would be a problem in the clinical use of the antibiotic While many patients receiving kanamycin exhibit evidence of mild renal irritation as manifested by cylindruria and occasionally albuminuria and microscopic hematuria the only clear cut evidence of serious renal toxicity was

sudden oliguria occurring in a patient reported by Berman and Katz[1] This patient recovered when the drug was withdrawn Renal clearance studies on patients receiving kanamycin revealed mild changes in one function or another in most patients [2] The significance of these changes has not been fully evaluated but serious renal toxicity must not be a frequent problem when one considers the fact that so few patients having moderate to severe degrees of renal failure prior to kanamycin therapy have shown evidence of aggravation of the disease with relatively large dosages of kanamycin Most patients with serious systemic diseases and often marked fluid and electrolyte disturbances have been treated with quite large dosages of kanamycin and none has developed more than transient increases in urine retention that could be attributed to the antibiotic

Skin rashes of the maculopapular type have occurred in association with kanamycin therapy but in most instances they have been so mild that it has not been necessary to stop the drug Eosinophilia (6 to 20 per cent) has been noted with some frequency but is apparently of no clinical importance[4] No other changes in the hematopoietic system liver function or electrocardiogram have been described

SUMMARY

Kanamycin appears to be one of the most effective antistaphylococcal antibiotics available today It has the advantage of being active against all strains of staphylococci is bactericidal in its effect and is absorbed rapidly after intramuscular administration (so important in pediatric practice) It has the disadvantage of producing acoustic nerve injury when it is administered for long periods of time or when extremely high blood levels are maintained for short periods of time Nephrotoxicity has not been a frequent serious complication but it is a potential hazard associated with the administration of kanamycin

Kanamycin has been administered successfully in virtually every known staphylococcal infection In many instances its effect has been dramatic and lifesaving but when the causative organism occurs in avascular areas systemic administration will not usually eradicate the staphylococci and surgical therapy must be used as a supplement to antibiotic therapy

Because of the toxicity associated with intense or prolonged use of kanamycin it should not be used in mild or self limited infections but it should not be withheld in moderately severe or severe infections

BIBLIOGRAPHY

1 BERMAN L B AND KATZ S Kanamycin nephrotoxicity Ann New York Acad Sc 76 149 156 1958

2 BLAU S AND KANOF N B Kanamycin (topical) in pyodermas Ann New York Acad Sc 76 278–229 1958
3 BOWEN J F JONES J M NASH E S RILEY E A SIMPSON D G AND MC CLEMENT J H Clinical experiences with kanamycin in chronic pulmonary tuberculosis Ann New York Acad Sc 76 163–166 1958
4 BUNN P A BALTCH A AND KRANJNYAK O Clinical experiences with kanamycin Ann New York Acad Sc 76 109–121 1958
5 CHALMERS T C SEBESTYEN K AND TIMBERLAKE W H The effect of kanamycin on the mental and electroencephalographic abnormalities and tremor in cirrhosis and pulmonary emphysema Ann New York Acad Sc 76 188–196 1956
6 COHN I JR Kanamycin for bowel sterilization Ann New York Acad Sc 76 212–?4 1958
7 CRON M J FARDIG O B JOHNSON D L PALERMITI F M SCHMITZ H AND HOOPER I R The chemistry of kanamycin Ann New York Acad Sc 76 27 1958
8 DONOMAE I CHAIRMAN Clinical studies of kanamycin treatment of pulmonary tuberculosis Ann New York Acad Sc 76 166–187 1958
9 DUTCHER J D Chemical and physical properties of neomycin *In* WAKSMAN S A EDITOR Neomycin Its Nature and Practical Application Baltimore Williams & Wilkins Co 1958 p 76
10 FALOON W W AND FISHER C J The effect of kanamycin on blood ammonia levels in cirrhosis Ann New York Acad Sc 76 196–203 1958
11 FINEGOLD S M WINFIELD M E ARONSOHN R B HEWITT W L AND GUZE L B Clinical experience with kanamycin Ann New York Acad Sc 76 319–347 1958
12 FINLAND M CONSULTING EDITOR The basic and clinical research of the new antibiotic kanamycin Ann New York Acad Sc 77 17–408 1958
13 GOUREVITCH A HUNT G A AND LEIN J Antibacterial activity of kanamycin Antib & Chemo 8 149–159 1958
14 GOUREVITCH A ROSSOMANO V Z PUGLISI T A TYNDA J M AND LEIN J Microbiological studies with kanamycin Ann New York Acad Sc 76 31–34 1958
15 HAWKINS J E JR The pharmacology of neomycin *In* WAKSMAN S A EDITOR Neomycin Its Nature and Practical Application Baltimore Williams & Wilkins Co 1958 p 130
16 HEWITT W L AND FINEGOLD S M Laboratory studies with kanamycin Ann New York Acad Sc 76 122–128 1958
17 HIGH R H SARRIA A AND HUANG N N Kanamycin in the treatment of infections in infants and children Ann New York Acad Sc 76 289–307 1958
18 HUNT G A AND MOSES A J Kanamycin treatment of experimental infections in mice Ann New York Acad Sc 76 81–88 1958
19 KUNIN C M AND FINLAND M Susceptibility and cross resistance of bacteria to streptomycin neomycin paromomycin and kanamycin Ann New York Acad Sc 76 42–44 1958
20 RUTENBURG A M KOOTA G M AND SCHWEINBURG F B The efficacy of kanamycin in the treatment of surgical infections Ann New York Acad Sc 76 348–362 1958
21 SANCHEZ F R AND SANCHEZ A R Kanamycin in anthrax typhoid paratyphoid and brucellosis Ann New York Acad Sc 76 235–242 1958
22 SINFIELD M CRISP G O MAXWELL M H AND KLEEMAN C R Nephrotoxic effects of kanamycin a preliminary report Ann New York Acad Sc 76 140–148 1958
23 STEENKEN W JR MONTALBINE V AND THURSTON J R The antituberculous activity of kanamycin in vitro and in the experimental animal (guinea pig) Ann New York Acad Sc 76 103 109 1958
24 THURMAN W G AND PLATOU R V Some experiences with kanamycin in the treatment of Salmonella and Shigella infections Ann New York Acad Sc 76 230–235 1958
25 TISCH D E HUFTALEN J B AND DICKISON H L Pharmacological studies with kanamycin Ann New York Acad Sc 76 44–65 1958
26 UMEZAWA H Kanamycin its discovery New York Acad Sc 76 20 1958
27 UMEZAWA H UEDA M MAEDA K YAGISHITA K KONDO S OKAMI Y NITTA K AND TAKEUCHI T Production and isolation of a new antibiotic kanamycin J Antib Japan ser A 10 181 1957
28 UNGER A M Personal communication 1958

sudden oliguria occurring in a patient reported by Berman and Katz[1] This patient recovered when the drug was withdrawn Renal clearance studies on patients receiving kanamycin revealed mild changes in one function or another in most patients [2] The significance of these changes has not been fully evaluated but serious renal toxicity must not be a frequent problem when one considers the fact that so few patients having moderate to severe degrees of renal failure prior to kanamycin therapy have shown evidence of aggravation of the disease with relatively large dosages of kanamycin Most patients with serious systemic diseases and often marked fluid and electrolyte disturbances have been treated with quite large dosages of kanamycin and none has developed more than transient increases in urine retention that could be attributed to the antibiotic

Skin rashes of the maculopapular type have occurred in association with kanamycin therapy but in most instances they have been so mild that it has not been necessary to stop the drug Eosinophilia (6 to 20 per cent) has been noted with some frequency but is apparently of no clinical importance[4] No other changes in the hematopoietic system liver function or electrocardiogram have been described

SUMMARY

Kanamycin appears to be one of the most effective antistaphylococcal antibiotics available today It has the advantage of being active against all strains of staphylococci is bactericidal in its effect and is absorbed rapidly after intramuscular administration (so important in pediatric practice) It has the disadvantage of producing acoustic nerve injury when it is administered for long periods of time or when extremely high blood levels are maintained for short periods of time Nephrotoxicity has not been a frequent serious complication but it is a potential hazard associated with the administration of kanamycin

Kanamycin has been administered successfully in virtually every known staphylococcal infection In many instances its effect has been dramatic and lifesaving but when the causative organism occurs in avascular areas systemic administration will not usually eradicate the staphylococci and surgical therapy must be used as a supplement to antibiotic therapy

Because of the toxicity associated with intense or prolonged use of kanamycin it should not be used in mild or self limited infections but it should not be withheld in moderately severe or severe infections

BIBLIOGRAPHY

1 BERMAN L B AND KATZ S *Kanamycin nephrotoxicity Ann New York Acad Sc* 76 149–156 1958

Chapter VIII | Recapitulation and Discussion

Maxwell Finland
Associate Professor of Medicine Harvard Medical School
Associate Director Thorndike Memorial Laboratory and
Physician in Chief Fourth Medical Service
Boston City Hospital Boston Mass

As the titles of this volume and the preceding chapters suggest the major concern here has been with an up to-date evaluation of the place of currently available antibiotics in the treatment and control of staphylococcal infections The individual contributors have dealt in greater detail with some of the anti biotics that have been most recently introduced and have attempted to summa rize the available information about these antibiotics not only as they concern staphylococcal infections but in regard to their usefulness in other infections as well In the opening chapter an attempt was also made to present a brief picture of the current problem of staphylococcal infections in general and the place of certain of the earlier antibiotics in their management

THE STAPHYLOCOCCUS PROBLEM

The *Staphylococcus* problem is an old and important one but it has recently been brought into focus by a number of events Perhaps the most dramatic of these have been the reports of a number of epidemics in hospital nurseries which resulted in a large morbidity and a significant mortality among newborn infants and in the transmission of the staphylococcal infections to many of their mothers Although the occurrence of epidemics of infections including staphylococcal infections in hospital nurseries was certainly not new and the

29 WELCH H WRIGHT W W WEINSTEIN H I AND STAFFA A W *In vitro* and pharmacological studies with kanamycin Ann New York Acad Sc 76 66–80 1958
30 WHITE A AND KNIGHT V Kanamycin pharmacological microbiological and clinical observations Ann New York Acad Sc 76 277–288 1958
31 WRIGHT K W RENZETTI A D JR. LUNN J AND BUNN P A Observations on the use of kanamycin in patients in a tuberculosis hospital Ann. New York Acad. Sc 76 157–163 1958
32 YANAGISAWA K KANAI K SATO N HASHIMOTO T AND TAKAHASHI H Effects of kanamycin in experimental tuberculosis of guinea pigs Ann. New York Acad. Sc 76 88–103 1958
33 YOW E M AND MONZON O T Laboratory and clinical evaluation of kanamycin in resistant bacterial infections Ann New York Acad Sc 76 372–390 1958
34 YOW M D AND WOMACK G K The use of kanamycin in staphylococcal epidemic in infants and children Ann New York Acad Sc 76 363–371 1958

more evident the situations that may always have been in existence but were submerged or not acknowledged

8 Laboratory facilities are becoming more widely available and more efficient these permit the recognition of the causative agents their susceptibility to antibiotics and now also their phage patterns allowing better diagnostic and epidemiological evaluations

9 Increasing numbers of research projects had been focusing attention on the problem of staphylococcal infections even before the current increase in interest among hospitals and other health agencies and in the lay press this increased interest has extended to the biology of the organisms and the various factors related to their virulence the problems of host resistance the epidemiology of staphylococcal infections and their prevention and treatment especially with antimicrobial agents and particularly within hospitals

The problem is further complicated by the ubiquity of the organism in man and his environment the multiplicity of ways it can spread and disseminate (patients carriers fomites air droplets etc) the hardy nature of the organism and most important the lack of precise information about many aspects of staphylococcal infections and how to cope with them Little indeed is known of how infectious the environmental organisms are what accounts for the virulence of certain strains their contagiousness and the effects of other ecological factors From the point of view of the host certain predisposing factors have been recognized such as diabetes general debility local trauma foreign bodies the use of hormones irradiation antibiotic prophylaxis and certain specific infections e g influenza However little is known about the factors that make otherwise normal persons susceptible or why the great majority of people both well and sick resist such infections with the same contagious strains

The solution(s) to the staphylococcal problem are obviously complex and are not likely to be found in any simple formula The infection can hardly be expected to yield to measures such as those adopted for intestinal infections like typhoid fever The introduction of barrier nursing for all patients with every type of staphylococcal infection including those who are only carriers would be a valuable aid but this is hardly feasible even in the most heavily staffed hospitals Even a minor approach to this method of attack would scarcely be possible in the great majority of hospitals in this country they are already plagued by a great scarcity of nursing and attending personnel and costs are already reaching a point where hospitals can hardly afford increases in their staff even if it were possible to enlist more people for that purpose The recognition and elimination of carriers particularly the so called dangerous carriers though occasionally successful at least temporarily again is a difficult problem in the state of our knowledge because of the large number of people involved nearly all of whom are essential in the conduct of everyday

extent of these epidemics not unusual they acquired new significance because of several circumstances

1 All but a small percentage of babies in the United States and probably also in large centers of population in many other countries are now born in hospitals

2 Many of the outbreaks of staphylococcal infections in nurseries occurred within a brief period and were recognized by bacteriophage typing as being caused by staphylococci belonging to a single phage type this was a new type not previously recognized and since the epidemics had occurred in widely scattered communities in many countries throughout the world they were considered to be in the nature of a pandemic

3 The *Staphylococcus* causing the epidemic in most of the hospitals was insensitive to the antibiotics that had been most widely used in those hospitals This same *Staphylococcus* was found to be the cause of many other hospital acquired infections it also appeared to be increasing in incidence along with other antibiotic resistant staphylococci and causing infections in many communities outside of hospitals

4 Reviews of the status of staphylococcal infections in many hospitals brought about an awareness of the fact that these were unusually frequent particularly among hospital acquired infections complicating surgery and in those occurring as secondary or terminal infections in patients with debilitating diseases or after apparent recovery from other infections under appropriate treatment with antibiotics

5 Other infections notably those caused by hemolytic streptococci that in previous (preantibiotic) years had been more frequent and more serious causes of hospital acquired infections had been nearly eliminated this gave greater relative prominence to the staphylococcal infections

6 Whereas in other infectious conditions notably meningococcal meningitis gonorrhea tuberculosis syphilis pneumonia and hemolytic streptococcal infections the use of antibiotics continued to be highly successful the over all results of antibiotic treatment of staphylococcal infections though at first very encouraging now were becoming quite disappointing this was especially true in the most serious of these staphylococcal infections namely those involving septicemia pneumonia or meningitis

7 The increasing use of hospitals for teaching has resulted in improvement of facilities for recognizing infections for the keeping processing and study of hospital records and for the over all use of hospitals for diagnosis and treatment This is true not only in hospitals affiliated with medical schools but in increasing numbers of nonaffiliated hospitals which are competing for medical interns and residents and which now also provide continuous educational programs for their attending and house staffs This in turn has led to better and more honest recording as well as self appraisal and has merely made

tions Indeed they were the only useful antimicrobial agents available for systemic use against staphylococcal infections before the discovery of penicillin Some reduction in mortality from serious infections with bacteremia had been reported from their use at that time In recent years these drugs have for the most part proved ineffective against serious staphylococcal infections especially those acquired in hospitals and most of the staphylococci from such infections are resistant to sulfonamide drugs The value of these agents as adjunctives to increase the activity of other antistaphylococcal antibiotics or to prevent the development of resistance to them has not been adequately demonstrated

Carbomycin and Spiramycin Carbomycin was the first erythromycin related antibiotic to be introduced It proved to be active against staphylococci in vitro and showed complete cross resistance with erythromycin on organisms made resistant to either one of these agents in the test tube but erythromycin resistant strains isolated from patients showed irregular susceptibility to carbomycin This antibiotic proved essentially to have very low activity against serious staphylococcal infections and therefore is no longer used for that purpose

Spiramycin is another erythromycin like antibiotic that is being used in some European countries It too is related to erythromycin in that organisms made resistant in vitro to either one of these agents show complete resistance to the other and also to carbomycin and to oleandomycin Although there are some reports of the successful use of spiramycin in the treatment of various infections with gram positive organisms the results in staphylococcal infections have not been impressive and this agent has not received acceptance in the United States Its extensive use in one large clinic has resulted in rapid dissemination of strains resistant to both spiramycin and erythromycin A second clinical trial was made some time later in the same clinic and spiramycin was then used intensively but only in combination with novobiocin The appearance and increase in incidence of staphylococci resistant to both of these antibiotics and to erythromycin were demonstrated although somewhat delayed as compared with the previous period when spiramycin was used alone Its in vitro activity against staphylococci is much less than that of either erythromycin or oleandomycin but the producers claim a relatively greater in vivo activity

Streptogramin (Staphylomycin) and Others Streptogramin and a group of similar antibiotics appear to be highly active agents against staphylococci in vitro but have had only minor study as yet in this country These studies have demonstrated some degree of cross resistance with the erythromycin related group of antistaphylococcal agents but not complete cross resistance These antibiotics have not received clinical trial or use in this country and only a few reports of their use abroad are available

activities of the hospital The environmental factors involved in the dissemination of dangerous organisms apply to many pathogens but are particularly applicable to staphylococci Attacks on these and similar fronts are important and will undoubtedly bring about alleviation of the problem In the meantime it becomes necessary to live with the problem and to attempt to minimize its serious effects while searching for better methods of attack on the over all situation

This book was not intended as a review of all the possible solutions that have been suggested or even of the many specific problems that require study before such solutions can be found The entire subject has been discussed in several recent symposia some of which have been published The reader is referred to the monograph on staphylococcal infections published in 1956 in the *Annals of the New York Academy of Sciences* (65 57–246) to the report of the Proceedings of the National Conference on Hospital Acquired Staphylococcal Disease held in Atlanta Georgia Sept 15–17 1958 and sponsored by the U S Public Health Service Communicable Diseases Center and National Academy of Sciences National Research Council and to the collection of papers entitled *Selected Materials on Staphylococcal Disease October 1958* issued by the U S Department of Health Education and Welfare Public Health Service Bureau of State Services Communicable Disease Center, Atlanta Georgia (Public Health Service Publication no 627) A brief summary of the clinical problems was presented by Rogers in the April 1958 issue of *D M* (*Disease a Month* Chicago, Year Book Publishers Inc)

MISCELLANEOUS ANTISTAPHYLOCOCCAL ANTIBIOTICS

The preceding chapters have presented a review of the information about available antibiotics and how they can best be used to minimize the hazards of staphylococcal infections once they occur Only those antibiotics that have proved useful in the treatment of staphylococcal infections have been dealt with A few other drugs will be discussed briefly here

Tyrothricin Tyrothricin was the first modern antibiotic to be made available It is still listed in *New and Nonofficial Remedies* for 1959 This antibiotic is active against all gram positive organisms including staphylococci but it is highly toxic to tissues and cannot be used systemically Its use is limited to local application in surface infections and it is still being made available either alone in solutions or troches or in various mixtures with other agents for topical application However there is very little information available about its value in staphylococcal infections

Sulfonamide Drugs Some of the sulfonamide drugs notably sulfathiazole and sulfadiazine exhibit considerable antistaphylococcal activity in vitro and have been found to be of some value in the treatment of staphylococcal infec

graphs to offer some comparisons of the available antistaphylococcal antibiotics in certain important respects these comparisons can only be considered as rough and qualitative It is doubtful whether agreement could be reached by many experienced investigators in all instances These comparisons may be of value as a summary and guide to the application of the agents that have been discussed in detail Some that have been mentioned only briefly namely the tetracyclines neomycin and streptomycin will also be included in these comparisons because they too may still have an important place in antistaphylococcal therapy at the present time

Relative Activity Comparisons of the activity of different antibiotics against staphylococcal infections in human beings are for the most part crude and only subjective because controlled clinical studies aimed at such comparisons are not available and are difficult if not impossible to carry out Moreover as already indicated determination of the relative value of antibiotics will depend on the experience of the individual making the comparison or on an assessment of reports of others as interpreted through one s own experience Bearing this in mind and considering only the activity in infections to which the causative organism is still fully sensitive it is still possible to consider penicillin erythromycin * novobiocin vancomycin kanamycin ristocetin and oleandomycin* as the most active more or less in that order The tetracyclines chloramphenicol bacitracin streptomycin and neomycin are probably less active and again approximately in that order

Kirby has considered vancomycin to be the most active and useful antibiotic for serious infections because of its bactericidal effect because of his failure to find strains resistant to it and because levels of activity can be assured since the intravenous route must be used Those who have had experience with this drug would probably concur in this view More generally it may be said that in serious hospital acquired staphylococcal infections that are resistant to penicillin erythromycin and novobiocin the drugs of choice would be vancomycin ristocetin and kanamycin more or less in that order Neomycin obviously is less useful though somewhat more active in vitro than some other agents such as kanamycin and streptomycin neomycin cannot be used systemically in a dosage adequate to produce a good clinical effect without serious toxicity Occasional brilliant results have been obtained by courageous physicians who resorted to this antibiotic in desperate cases before kanamycin became available The latter antibiotic would now be preferred for systemic

---

In referring to the activity of erythromycin and oleandomycin for comparative purposes the activity of oral preparations is considered on the basis of erythromycin propionate and triacetyloleandomycin the best absorbed of these respective drugs (reports of comparisons of erythromycin stearate are not available) In vitro erythromycin is four to five times as active (on the average) as oleandomycin against strains susceptible to both

Leucomycin mentioned in the introductory chapter is now under study for both its in vitro and clinical usefulness It is highly active in vitro and shows some cross resistance with erythromycin and related antibiotics

Bryamycin is another antibiotic that is highly active against staphylococci in vitro It exhibits no cross resistance with any other antibiotics but it has not become available for clinical trial

COMPARISONS OF USEFUL ANTISTAPHYLOCOCCAL ANTIBIOTICS

As indicated in the previous chapters from a therapeutic point of view the situation is not altogether as gloomy as would appear from the foregoing paragraphs To be sure the mortality from certain types of staphylococcal infections remains high but this high mortality is limited to certain types of staphylococcal infections namely those accompanied by staphylococcal septicemia endocarditis pneumonia or meningitis among the pneumonias those occurring in infancy and those complicating influenza still have a particularly high mortality Poor results are also obtained in staphylococcal infections that complicate other debilitating diseases particularly when the treatment is undertaken late in the infection or when the antibiotics are not properly chosen or applied Even in these categories of severe and highly fatal infections encouraging results are reported with the new agents or even with the older ones when properly applied In the great majority of staphylococcal infections the results have been highly favorable

Although each of the authors who reviewed the individual antibiotics attempted to present a fair picture of the potentiality of that agent some have emphasized the more favorable aspects and others have perhaps gone into greater detail about the less favorable properties In each instance however the intent was to present the available information so that the reader could apply these facts most effectively Comparisons of these antibiotics are difficult for their effects depend on the judgment and care with which they are used and these in turn depend on experience Some physicians may extract the most value from relatively poor agents by applying them properly and to their best advantage whereas others may have less success in the application of more potent agents by using them improperly The excessive use of such antibiotics when they are not indicated inadequate dosage improper choice of cases failure to guard against development of resistance when possible failure to recognize mixed infections complicated infections or toxic effects of the antibiotics and failure to apply proper measures to cope with these situations all are factors that may reduce the value of even the most effective agents Moreover the failure to apply local treatment or to drain accessible foci of suppuration when possible likewise tends to diminish the effectiveness of the antibiotics against staphylococcal infections

In spite of these difficulties an attempt will be made in the next few para

novobiocin is also rising so that from 10 to 30 per cent or more may be highly resistant to one or another of these drugs Interestingly enough resistance of this degree to chloramphenicol has been rare even where this agent has been used extensively Although isolated instances have been reported where up to 50 per cent of chloramphenicol resistant staphylococci were encountered these occurred only during brief periods under special circumstances of inten sive usage of chloramphenicol as the only antibiotic when normal usage of chloramphenicol was resumed the incidence again dropped to low levels Thus far the incidence of strains of staphylococci resistant to the other antibiotics namely to bacitracin neomycin vancomycin kanamycin and ristocetin has remained exceedingly low In the case of some of these antibiotics notably chloramphenicol and vancomycin it appears to be more difficult in vitro to produce strains resistant to these antibiotics than is the case with others

Cross Resistance All of the tetracycline antibiotics (chlortetracycline oxytetracycline tetracycline and the most recent demethylchlortetracycline) exhibit *essentially complete cross resistance both in vitro and in vivo* Olean domycin spiramycin and carbomycin may be considered erythromycin related drugs organisms made resistant by subculture to any of these 4 antibiotics develop complete cross resistance to each of the others On the other hand strains isolated from patients exhibit cross resistance among these agents only irregularly at least in the usual sensitivity tests Among patho genic staphylococci isolated in various laboratories from 10 to 70 per cent of freshly isolated erythromycin resistant strains show resistance of moderate or high degree to oleandomycin as well and the same is probably true of carbomycin

There appears to be nearly complete cross resistance between neomycin and kanamycin both in organisms made resistant in vitro and in resistant strains isolated from patients who are under treatment with one or the other of these agents *There is also a minor degree of cross resistance between these* two agents and streptomycin but this is probably of little or no clinical sig nificance Likewise there is some slight degree of cross resistance between the tetracyclines and chloramphenicol and this also probably has no clinical significance

None of the other antibiotics namely penicillin novobiocin bacitracin vancomycin or ristocetin show any cross resistance among each other or with any of the other antibiotics No other cross resistance of importance has been found between the tetracyclines and any other group of antibiotics or between each of the erythromycin like antibiotics and others not in that group except for minor cross resistance between these agents and antibiotics of the strepto gramin group

Bacteriostatic vs Bactericidal Action Each of the antibiotics we have con sidered may be bactericidal under certain circumstances and the antistaphylo

use Other considerations may make some of the antibiotics relatively more effective than indicated here under special circumstances

Moreover the effectiveness of some of these agents in serious staphylococcal infections depends on their use together with other active agents either because of their bacteriostatic action or because of the tendency of the organ ism to become resistant in the course of treatment Thus erythromycin novo biocin oleandomycin and streptomycin should probably never be used alone in serious staphylococcal infections where treatment must be continued for relatively long periods Another antibiotic notably bacitracin kanamycin or chloramphenicol may well be used as a second antibiotic to prevent the development of resistance or at least to delay the appearance of resistant vari ants and depress the degree of resistance that might emerge In fact bacitracin though not very effective when used alone in the treatment of serious staphy lococcal infections may be highly useful in increasing the activity of novo biocin or erythromycin or even vancomycin likewise chloramphenicol has its greatest usefulness in staphylococcal infection in combination with more active agents particularly erythromycin and novobiocin by itself it has rela tively low activity

Resistance When each of the antibiotics was first introduced its activity against different strains of staphylococci isolated from patients before treat ment was started was more or less uniform such variations as were observed were over a relatively narrow range of concentrations of the antibiotic With increasing usage however progressively larger proportions of strains with moderate or high resistance to certain of these antibiotics have been encoun tered This is particularly true in regard to penicillin streptomycin and the tetracyclines In many places where they have been extensively used either in the hospital or in the community this is now also being observed with respect to erythromycin oleandomycin and novobiocin as well For each of these antibiotics a certain proportion of strains of staphylococci are now found to be highly sensitive nearly all of the rest are highly resistant and a relatively small proportion (perhaps 2 to 10 per cent of the total) are found to be inter mediate in their susceptibility (i e only slightly sensitive or moderately resistant)

The proportion of strains resistant to each of these antibiotics will vary with the hospital or community For example strains resistant to 50 units of penicillin or more may comprise as many as 50 per cent of all pathogenic strains and in some hospitals even more than 80 per cent of the staphylococci isolated from infections or from nasal carriers in those hospitals For the tetracyclines the proportion of staphylococci resistant to 50 μg or more may range from 20 to more than 50 per cent for a similar concentration of strepto mycin the proportion may range from 20 to more than 90 per cent resistant In some hospitals the incidence of strains resistant to erythromycin and to

orally or parenterally as much as 100 million units/day or more has been used in the treatment of infections with penicillin resistant strains In general dosages of 2 to 10 million units/day are now generally given for the treatment of infections with highly or moderately sensitive staphylococci All other antibiotics have a relatively narrow range of dosage the usual dosage is about 2 Gm /day but larger dosages of erythromycin novobiocin oleandomycin and chloramphenicol—up to 4 Gm daily by mouth—may be given The larger dosages of erythromycin however may produce gastrointestinal irritation in some patients and the larger dosages of chloramphenicol may produce sore tongue and gastric irritation

When given orally neomycin and kanamycin may be used in daily dosages of 4 to 6 Gm however 8 or even 12 Gm /day has been used in the treatment of patients with impending hepatic coma but the larger dosages of these two drugs may produce vomiting and diarrhea in some patients Except in unusual circumstances intramuscular dosage of neomycin should not exceed 1 Gm daily and this should not be given for more than one week Dosage of kanamycin is best kept at 1 5 Gm daily or less and it should be given for no longer than two weeks to avoid serious renal damage and ototoxicity The dosage of streptomycin should likewise be kept at or less than 2 Gm daily at first and reduced later to 1 Gm /day The dosage of bacitracin is 80 000 to 100 000 units daily given in three or four injections Most of the drugs are given in two to four equal amounts over a 24 hour period The large doses of penicillin may be given by continuous intravenous infusion and this method has been employed although it is not recommended for vancomycin and ristocetin The dosages mentioned are recommended as average for adults and should be adjusted for infants and children

Toxicity Most of these antistaphylococcal antibiotics are relatively free of serious toxic effects but some have individual propensities to produce certain specific untoward effects which must be considered either in the choice of the drug for therapy or in evaluating fever and unusual symptoms while they are being given In each instance it is essential to be on the watch for some of them by close clinical observation or by employing the proper laboratory or other tests

In general penicillin is the least toxic of the antibiotics even when given in large dosages however there has been an increasing number of persons who have acquired serious hypersensitivity to this drug which may exclude its use or require its discontinuance The serum sickness type of sensitivity reaction is characteristic of penicillin but it has also been reported with novobiocin The latter antibiotic and streptomycin may produce fever and rashes novobiocin perhaps more frequently than any other antibiotic during the course of treatment These drug fevers and rashes usually clear up within one to four days after treatment has stopped Some of the erythematous reactions that

coccal antibiotics may be classified roughly according to their activity some being predominantly bactericidal and others largely bacteriostatic Thus considering activity against only sensitive strains penicillin streptomycin kanamycin neomycin bacitracin vancomycin and probably ristocetin are generally classified as predominantly bactericidal agents On the other hand the tetracycline antibiotics chloramphenicol novobiocin erythromycin and oleandomycin are said to be bacteriostatic in their action The antibiotics classified as bacteriostatic may exert a bactericidal effect on organisms that are moderately sensitive to them if high enough concentrations of the antibiotic can be achieved For certain strains of staphylococci and perhaps for many strains with some combinations the use of a predominantly bactericidal drug in combination with one that is predominantly bacteriostatic may increase the total bactericidal effect against the organism however this activity cannot always be depended on to act in a predictable manner The difference between the bactericidal and bacteriostatic end points may vary with the conditions of the test in either type of agent but the difference in the concentrations is of course generally small for the bactericidal agents regardless of the methods used

Absorption and Route of Administration Penicillin erythromycin novobiocin the tetracyclines chloramphenicol and oleandomycin are absorbed from the gastrointestinal tract and may also be given by the intramuscular or intravenous routes On the other hand streptomycin bacitracin vancomycin kanamycin neomycin and ristocetin are not absorbed from the gastrointestinal tract Oral use of the latter group of agents is therefore limited to their expected effects on the intestinal flora as in the preparation for large bowel surgery or in the prevention or treatment of staphylococcal enterocolitis Neomycin and kanamycin are now the antibiotics most frequently used for the former and the same antibiotics or erythromycin or bacitracin have been used for the latter but vancomycin and ristocetin could also be used orally in the prevention or treatment of staphylococcal enterocolitis The systemic use of streptomycin bacitracin kanamycin and neomycin is limited to intramuscular injection because they are probably too toxic when given intravenously Vancomycin and ristocetin are given only intravenously the currently available intramuscular preparations are too irritating but improved preparations may be available for such use in the future All of the antistaphylococcal antibiotics may be used topically on surface lesions of the skin and mucous membranes or may be injected into purulent foci in appropriate amounts and concentrations However the application of penicillin streptomycin and novobiocin to lesions of the skin and mucous membranes is not recommended because of the high potential of sensitizing effects of these drugs (known for the first two and presumed for novobiocin)

Dosage Penicillin can be given within a very wide range of dosage either

toxicity such as fever and rash has appeared hepatotoxicity has also been reported in patients on prolonged therapy with streptomycin but this too is very rare In patients receiving novobiocin a yellow tinge to the skin sclera and mucous membranes has been noted in such instances the serum gives only a positive direct reaction in the test for bilirubin and this is said to be due to some metabolic product of novobiocin there is no bile in the urine in such cases

Optimum Therapy In order to achieve the best results in the treatment of staphylococcal infections it is essential to abide by certain obvious principles First it is important to treat only infections that are either (1) extensive (2) large and spreading (3) multiple (4) associated with blood stream invasion or (5) in locations that make them serious Antibiotics should generally be avoided in simple small furuncles that are well localized The antibiotics should be selected on the basis of susceptibility of the offending *Staphylococcus* It is best where conditions permit to have this information before selecting the agents However when immediate treatment seems imperative materials for culture and sensitivity testing should be obtained before institution of such treatment Under these conditions the drugs to be used should be chosen on the basis of the best probability in view of the most likely source of infection and the known susceptibility of the strains isolated in similar situations In all cases in which erythromycin novobiocin streptomycin or oleandomycin is chosen another agent that has been shown to be active against the offending organism or may be expected to be active should be used simultaneously If the second agent is discontinued or a change is necessary it is important to stop the first agent at the same time and to reinstitute treatment with two drugs again

Changes in therapy to the appropriate antibiotic if the original choice was not proper may then be made when the results of the culture and sensitivity tests become available Changes should also be made when the patient fails to respond clinically or bacteriologically or shows clear signs of relapse of infection after apparent improvement but an ample time should be allowed to demonstrate such improvement since staphylococcal infections may resolve slowly and the symptoms subside gradually even when the proper antibiotics are chosen and are performing properly If a change in therapy is contemplated attempts should be made to obtain further material for culture and sensitivity tests and to look for changes in sensitivity of the strains and the appearance of new strains of other (super)infections The possibility of fever resulting from the drug must be considered especially when either penicillin streptomycin or novobiocin is used such fever usually subsides after withdrawal of the offending drug

Early drainage of accessible foci of suppuration should be undertaken Aspiration may be used in the case of infection of serous cavities and surgical

occur during the second week of novobiocin treatment may clear during continued administration of this agent but it is generally not advisable to keep giving any drug in the face of a rash and a febrile reaction except in unusual circumstances

Any of the antibiotics may produce gastrointestinal irritation during oral administration if the dosage is large enough The tetracyclines or erythromycin when given in a dosage of 2 Gm /day or more may do this there may be nausea, feeling of flatulence distention and increased bowel activity in the form of large bulky soft stools or occasionally diarrhea These symptoms may also be encountered in patients who receive kanamycin or neomycin in a dosage greater than 6 Gm /day by mouth

Changes in the flora of the respiratory or intestinal tract may result from the use of any of the antibiotics given by any route but particularly when given orally Strains of staphylococci resistant to the antibiotics used may become prominent and give rise to new infections or to relapses Gram negative bacillary forms (*Escherichia coli Aerobacter aerogenes Proteus* and *Pseudomonas*—and occasionally *Achromobacter*) may replace the predominant gram positive flora when antibiotics with narrow or intermediate spectrum are used and yeasts or fungi may increase and assume pathogenic significance when broad spectrum antibiotics (tetracyclines chloramphenicol kanamycin neomycin) or multiple antibiotics are employed for long periods

Local irritation at the sites of intramuscular injection varies in intensity and the same is true of local venous irritation at the site of intravenous injections or infusions This may vary with the drug used the concentration of the antibiotic that is injected or the speed with which the injection is made Occasional thermal reactions have occurred after intravenous injections of vancomycin but these have been less frequent with recent lots

Renal irritation occurs only after injection of neomycin kanamycin or bacitracin the severity of these reactions being essentially in that order these three drugs should be avoided or used with great caution in patients with impaired renal function Streptomycin and vancomycin also should be used with caution in patients with renal insufficiency these two antibiotics as well as kanamycin and neomycin may give rise to eighth nerve toxicity which may be exaggerated by the increased retention of the drug that occurs in patients with impaired renal function

Granulocytopenia has been reported from streptomycin novobiocin and chloramphenicol thrombocytopenia has been observed with ristocetin and chloramphenicol and aplastic anemia has been attributed to the latter antibiotic in a number of cases All of these hematological complications however are quite rare Hepatotoxicity likewise is very infrequent and is limited to rare cases in which large dosages of tetracyclines are injected intravenously or to patients who continue to receive novobiocin after other evidence of drug

toxicity such as fever and rash has appeared hepatotoxicity has also been reported in patients on prolonged therapy with streptomycin but this too is very rare In patients receiving novobiocin a yellow tinge to the skin sclera and mucous membranes has been noted in such instances the serum gives only a positive direct reaction in the test for bilirubin and this is said to be due to some metabolic product of novobiocin there is no bile in the urine in such cases

Optimum Therapy In order to achieve the best results in the treatment of staphylococcal infections it is essential to abide by certain obvious principles First it is important to treat only infections that are either (1) extensive (2) large and spreading (3) multiple (4) associated with blood stream invasion or (5) in locations that make them serious Antibiotics should generally be avoided in simple small furuncles that are well localized The antibiotics should be selected on the basis of susceptibility of the offending *Staphylococcus* It is best where conditions permit to have this information before selecting the agents However when immediate treatment seems imperative materials for culture and sensitivity testing should be obtained before institution of such treatment Under these conditions the drugs to be used should be chosen on the basis of the best probability in view of the most likely source of infection and the known susceptibility of the strains isolated in similar situations In all cases in which erythromycin novobiocin streptomycin or oleandomycin is chosen another agent that has been shown to be active against the offending organism or may be expected to be active should be used simultaneously If the second agent is discontinued or a change is necessary it is important to stop the first agent at the same time and to reinstitute treatment with two drugs again

Changes in therapy to the appropriate antibiotic if the original choice was not proper may then be made when the results of the culture and sensitivity tests become available Changes should also be made when the patient fails to respond clinically or bacteriologically or shows clear signs of relapse of infection after apparent improvement but an ample time should be allowed to demonstrate such improvement since staphylococcal infections may resolve slowly and the symptoms subside gradually even when the proper antibiotics are chosen and are performing properly If a change in therapy is contemplated attempts should be made to obtain further material for culture and sensitivity tests and to look for changes in sensitivity of the strains and the appearance of new strains of other (super)infections The possibility of fever resulting from the drug must be considered especially when either penicillin streptomycin or novobiocin is used such fever usually subsides after withdrawal of the offending drug

Early drainage of accessible foci of suppuration should be undertaken Aspiration may be used in the case of infection of serous cavities and surgical

incisions may be made in the case of lesions of the skin and subcutaneous tissues or where there are large walled off suppurative foci that do not respond to systemic treatment The use of lytic enzymes such as streptokinase and streptodornase or trypsin may be resorted to when there are large deposits of fibrin these may be helpful particularly in the pleural cavity and sometimes in the joints or the pericardium Topical instillations of antibiotics in accessi ble infected cavities should be employed whenever feasible bacitracin is probably the most useful for this purpose but sensitizing agents such as peni cillin streptomycin and probably novobiocin should be avoided in topical therapy of lesions of the skin or mucous membranes

Reservations or Limitations of Antibiotics The problem of restricting one or another antibiotic has not been discussed thus far Several methods have been recommended

1 Limiting the use of one or more agents to life threatening infections in which they are the only effective ones as judged from sensitivity tests would be expected to preserve the drug for such cases by reducing the chances for development and spread of variants resistant to that drug

2 Rotation of drugs some being used for several months and then with drawn completely from use and replaced by others would be expected to limit the extent to which resistant variants would occur and spread and such resistance as will have occurred would then be expected to be dissipated in time after the withdrawal of that agent and the introduction of others

3 Some agents might be restricted to use only in combination with other antibiotics only those to which the causative organisms are sensitive being used in such combinations This would be expected to delay the emergence of resistance and perhaps to result in a lower degree of resistance when it develops

These restrictions would of course be applicable only to the use of anti biotics to which the incidence of resistant strains is already appreciable or to which resistance may be expected to develop in the course of their use The efficacy of any of these methods has not been fully documented and they cannot therefore be recommended on the basis of proved usefulness

The most reasonable restriction in the use of antistaphylococcal antibiotics that can be recommended without hesitation is that they be used sensibly and only for clearly defined indications These antibiotics should never be used for prophylaxis on a wide scale in hospitals or in closed communities particularly for long periods Such usage is certain to upset the balance of the prevailing flora in favor of organisms resistant to the very antibiotics that are so used The antibiotics most suitable for each case should be selected and changes made after adequate trial has shown them to be ineffective or inadequate or when other infections are demonstrated or when evidence of toxicity pre cludes their further use

INDEX

INDEX